Respiratory Medicine (2011) 105, 259–265

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Three-year dispensing patterns with long-acting inhaled drugs in COPD: A database analysis

Fernie Penning-van Beest [a,*], Myrthe van Herk-Sukel [a], Rupert Gale [b], Jan-Willem Lammers [c], Ron Herings [a,d]

[a] PHARMO Institute, PO Box 85222, 3508 AE Utrecht, Utrecht, The Netherlands
[b] Novartis Horsham Research Centre, UK
[c] Department of Respiratory Medicine, University Medical Centre Utrecht, The Netherlands
[d] Department of Health Policy & Management, Erasmus University Medical Centre, Rotterdam, The Netherlands

Received 15 March 2010; accepted 9 July 2010
Available online 11 August 2010

KEYWORDS
COPD;
Long-acting inhaled drug;
Persistence;
Treatment pattern

Summary
Background: Long-acting muscarinic antagonists (LAMA), long-acting β2-agonists (LABA) and fixed dose combinations (FDC) of inhaled corticosteroids (ICS) and LABA are used as inhaled maintenance therapies for COPD.
Objective: To estimate persistence rates from dispensing patterns of long-acting inhaled drugs for COPD.
Methods: From the PHARMO-database, COPD patients starting LAMA, LABA or LABA-ICS FDC between 2002 and 2006 were selected. Persistence with the initial as well as with any long-acting inhaled drug was determined, defined as time between start and stop of initial/any therapy, allowing ≤60-days gaps between refills. For patients who did not continue to receive dispensings of the initial therapy for at least one year, the first change in therapy was determined.
Results: The study included 2201 LAMA, 1201 LABA and 4146 LABA-ICS FDC users. Persistence rates with initial therapy alone at 1, 2, and 3 years were 25%, 14%, 8% for LAMA, 21%, 10%, 6% for LABA and 27%, 14%, 8% for LABA-ICS FDC. Of patients who did not persist with LAMA alone for one year, 15% added and 13% switched therapy (both mostly LABA-ICS FDC). Of patients not persisting with LABA alone, 9% added therapy (mostly LAMA) and 31% switched therapy (mostly to LABA-ICS FDC). In patients not persisting with LABA-ICS FDC, add-on and switch occurred equally frequent (11%, mostly LAMA). Persistence rates with any long-acting drug at 1, 2 and 3 years were 36%, 23% and 17% respectively.
Conclusion: Persistence with the initial as well as with any long-acting inhaled drug in COPD is low, with a substantial proportion of patients changing therapy.

* Corresponding author. Tel.: +31 302345 162; fax: +31 302345 568.
E-mail address: fernie.penning@pharmo.nl (F. Penning-van Beest).

0954-6111/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.07.007

Introduction

According to the latest estimates of the World Health Organisation (WHO), 210 million people have chronic obstructive pulmonary disease (COPD) and 3 million people died of COPD in 2005. The WHO predicts that COPD will become the third leading cause of death worldwide by 2030.[1]

COPD cannot be cured, but pharmacological management aims to provide symptom control, improve health status and reduce exacerbations. Inhaled bronchodilators are key therapies in the management of COPD.[2] Short-acting bronchodilators increase exercise tolerance acutely and are often used as 'rescue' medication. Guidelines such as those produced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[2] recommend long-acting bronchodilators (either alone or in combination) as maintenance therapy in patients with moderate or severe disease (with moderate defined as an FEV1/FVC ratio of <0.70 and percent predicted FEV1 between 50 and 80%; and severe disease as FEV1/FVC <0.70 and predicted FEV1 between 30 and 50%). Such patients should also have access to pulmonary rehabilitation which offers a number of benefits and covers a range of non-pulmonary problems that may not be adequately addressed by medical therapy such as exercise de-conditioning. In the Netherlands, the long-acting β2-agonists (LABA) salmeterol and formoterol and the long-acting muscarinic antagonist (LAMA) tiotropium are available. Inhaled corticosteroids (ICS) are recommended in the GOLD guidelines as add-on therapy in the management of severe COPD patients with repeated exacerbations.[2] Fixed dose combinations (FDC) of LABA and ICS are available in the Netherlands as salmeterol-fluticasone propionate and formoterol-budesonide.

Since COPD is a chronic and progressive disease, the use of long-acting inhaled drugs is expected to be long-term. Adherence, however, is often problematic as a result of periods of symptom remission, the complexity of treatment regimens and administration, patients' perceptions of their illness and their understanding of the treatment.[3] Moreover, clinical efficacy of inhaled therapy is not always obvious for each patient. In addition, poor adherence to COPD management guidelines by physicians has been demonstrated.[3–5] It should be noted that adherence encompasses both compliance and persistence and this study only considers the latter. Studies from daily practice, including an earlier PHARMO study, have shown that persistence with long-acting inhaled drugs is low. Breekveldt-Postma et al. found that only 37% of new users of tiotropium, 13% of new LABA users and 17% of new LABA-ICS FDC users continued using this drug for at least one year.[6] In the study by Cramer et al. only 12–27% of patients starting on LAMA, LABA, or LABA-ICS FDC continued on the initial drug for more than one year.[7] As the aim of these studies was to compare different COPD drugs, persistence was restricted to the initial drug. Since patients with COPD cannot be cured and guidelines suggest either adding or changing therapy as the disease worsens, a better reflection of persistence with long-acting inhaled drug treatment is obtained when persistence is determined irrespective of the specific drug type. Therefore, the aim of our study was to determine persistence rates with the initial therapy as well as with any long-acting inhaled drug for COPD in daily practice up to three years after start. Moreover, changes in treatment during the first year of therapy were studied.

Methods

Setting

Data were obtained from the PHARMO medical record linkage system (PHARMO RLS), a population-based patient-centric data tracking system including high quality and complete information linked on a patient level of, among other things, patient demographics, drug dispensings and hospital morbidity of approximately 3 million community-dwelling inhabitants of 48 geo-demographic areas in the Netherlands. The drug dispensing histories contain data on the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and thus the duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge.

Study patients

From the PHARMO RLS, we first identified all new, probable COPD patients in the period of 2001–2006. New, probable COPD patients were identified as patients with a first dispensing for COPD therapy in the period of 2001–2006 (i.e. the index date) at the age of 55 or older, including: short-acting β2-agonists (SABA), LABA, short-acting muscarinic antagonists (SAMA), LAMA, LABA-ICS FDC, SABA-SAMA FDC, and xanthine derivatives. To ensure that COPD therapy was started at the age of 55 or above and to enhance the probability that a patient was treated for COPD instead of for asthma, patients had to have a registration in PHARMO RLS of at least two years before the index date and no dispensing for any drug for obstructive airway diseases or nasal corticosteroids in these years. Additionally, patients with a hospitalisation for asthma in the period of 1999–2007 were excluded from the COPD cohort. Moreover, patients were excluded if they were hospitalised for lung cancer, lung surgery, tuberculosis, sarcoidosis, lung fibrosis or pneumoconiosis in this period as these diseases can also demonstrate COPD-like symptoms.

From the COPD cohort, new users of LAMA, LABA or LABA-ICS FDC in the period 2002–2006, i.e. no use of these long-acting COPD drugs in 2001, were included in the study cohort. The date of the first dispensing for LAMA, LABA or LABA-ICS FDC was defined as study entry date. New users were only included if they had at least a second dispensing for any of the long-acting inhaled drugs within 180 days after study entry, started on monotherapy, i.e. LAMA only, LABA only or LABA-ICS FDC only, and had at least three years of follow-up after study entry. End of follow-up was the date of death, end of data collection (e.g. because the patient moved outside the PHARMO catchment area) or end of study period (31 December 2007), whichever came first.

Persistence

For each study patient, all dispensings for LAMA, LABA and LABA-ICS FDC during the three-year follow-up period were converted into treatment episodes of continuous use of respectively LAMA, LABA and LABA-ICS FDC, based on the method of Catalan.[8] A treatment episode was considered uninterrupted if the gap between dispensings was 60 days or less, as done by Cramer et al.[7] Otherwise, use of the drug class was considered interrupted, the respective treatment episode was ended and a next episode defined.

Persistence with the initial long-acting inhaled monotherapy, i.e. the number of days of continuous use including permissible gaps of maximally 60 days, was determined as the number of days from the start of this therapy (i.e. study entry date) to the end date of the first treatment episode or the start date of a dispensing of one of the other two long-acting inhaled drug classes, whichever occurred first. In addition to the persistence with the *initial* long-acting inhaled monotherapy, we also assessed the persistence with *any* long-acting inhaled drug, i.e. the number of days of continuous use of any long-acting inhaled drug from study entry date onwards including permissible gaps of maximally 60 days. In this analysis, all dispensings for LAMA, LABA and LABA-ICS FDC during follow-up were converted into treatment episodes of continuous use of any long-acting inhaled drug.

Treatment pattern

For study patients who did not persist with the initial monotherapy for at least one year, i.e. the number of days of continuous use including permissible gaps was less than 365, we determined whether they: 1) had switched to one of the other two long-acting inhaled drug classes, or 2) had an add-on of the other two long-acting inhaled drug classes, or 3) had no switch or add-on and restarted the initial drug class within 60 days, i.e. a second treatment episode of the initial drug class was started within 60 days after the end date of the first treatment episode, or 4) had no switch or add-on and stopped using the initial drug class for at least 60 days.

Switching was defined as starting one of the other two long-acting inhaled drug classes after the last dispensing within the first treatment episode of the initial drug class or within 60 days after the end of that episode. An add-on was defined as 1) starting one of the other two long-acting inhaled drug classes before the last dispensing within the first treatment episode of the initial drug class, or 2) starting one of the other two long-acting inhaled drug classes within 60 days after the end date of the first treatment episode of the initial drug class and restarting the initial drug at this date.

User type

In addition to the above mentioned dichotomous outcome 'persistent with *any* long-acting inhaled drug', study patients who were not classified as persistent for at least three years were further analysed to characterise the usage pattern of long-acting inhaled drugs in this expectedly large patient group. The following user types, based on all long-acting inhaled drug dispensings within three years of follow-up, were distinguished:

- regular users: patients with at least one discontinuation of their long-acting treatment for a period of 61 days of more, but no longer than 180 days;
- inconsistent users: patients with at least one discontinuation of their long-acting treatment for more than 180 days;
- short-term users: patients with dispensings for long-acting inhaled drugs in the first year only.

For these different types of users we determined their co-medication use during follow-up including oral corticosteroids, oral antibiotics and respiratory drugs besides long-acting drugs. This information on co-medications may help explain a patient's usage pattern of long-acting COPD drugs.

Analyses

All data were analyzed using SAS programs organised within SAS Enterprise Guide version 3.0 (SAS Institute Inc., Cary, NC, USA) and conducted under UNIX using SAS version 9.1. Persistence with treatment over time was analysed using Kaplan Meier survival analyses. As the study only included patients with at least three years of follow-up, persistence results may not be representative for all COPD patients. Therefore, a sensitivity analysis for one- and two year persistence with the initial monotherapy was performed including patients with at least one and two years of follow-up respectively (instead of the required three years). Similarly, changes in treatment were also determined in non-persistent patients with at least one year of follow-up. Rates of persistence with any long-acting inhaled drug after one, two and three years were determined separately for a subset of patients with a hospitalisation with a primary or secondary discharge diagnosis of COPD in their entire available history and follow-up in the PHARMO RLS. This sub-analysis was performed because selecting patients based on their drug use, as opposed to diagnoses which were not available in the dataset, means that we could not rule out that patients treated for diseases other than COPD were included in the study cohort. The subset of patients with a primary or secondary discharge diagnosis of COPD are most likely to have the disease. Please note, as mentioned above, this hospitalisation may have occurred before or after study entry and even after end of study follow-up. Furthermore, COPD was not necessarily the primary reason for hospitalisation.

Results

The COPD cohort included 54,807 patients. Of these, 28,462 patients (52%) were new users of LAMA, LABA or LABA-ICS FDC in the period 2002—2006; 17,371 patients had at least a second dispensing for any of the long-acting inhaled drugs within 180 days and 15,668 patients also started on monotherapy. The final study cohort included 7548 patients with at least three years of follow-up after study entry, i.e. 2201

patients starting on LAMA, 1201 patients starting on LABA and 4146 patients starting on LABA-ICS FDC. The use of these long-acting inhaled drugs was mostly initiated by a general practitioner (71–80% of patients, Table 1). In the year before start of LAMA, LABA or LABA-ICS FDC use, 30–52% of patients had used some other respiratory drug, 21–28% had used oral corticosteroids and 53–60% had used oral antibiotics. Co-morbidity was frequent among study patients: about 60% of patients had used drugs from at least four different drug classes (besides respiratory drugs) in the year before study entry.

Fig. 1 shows the proportion of patients who were still using the initial long-acting inhaled monotherapy over time. Persistence rates at 1, 2, and 3 years were 25%, 14% and 8% for LAMA, 21%, 10% and 6% for LABA and 27%, 14% and 8% for LABA-ICS FDC. Similar one- and two-year rates were observed in patients with at least one and two years of follow-up respectively (data not shown).

Of patients who did not persist with LAMA alone for at least one year ($n = 1643$), 15% added and 13% switched therapy (Table 2). The most frequently added long-acting inhaled drug class was LABA-ICS FDC, which was also the drug class patients most frequently switched to (70% of 240 add-ons and 74% of 206 switches). Of patients not persisting with LABA alone for one year ($n = 947$), 9% added therapy and 31% switched therapy. The most frequent add-on was LAMA (80% of 83 add-ons) and switches were mostly to LABA-ICS FDC (78% of 296 switches). In patients not persisting with LABA-ICS FDC alone ($n = 3027$), add-on and switch occurred with equal frequency (11%) and was mostly LAMA (92% of 335

Table 1 Characteristics of COPD patients starting use of long-acting inhaled monotherapy.

	Patients starting on LAMA $N = 2201$ n (%)	Patients starting on LABA $N = 1201$ n (%)	Patients starting on LABA-ICS FDC $N = 4146$ n (%)
Gender			
Men	1193 (54.2)	560 (46.6)	1980 (47.8)
Women	1008 (45.8)	641 (53.4)	2166 (52.2)
Age group (in years)			
55–64	574 (26.1)	382 (31.8)	1547 (37.3)
65–74	786 (35.7)	428 (35.6)	1482 (35.7)
≥75	841 (38.2)	391 (32.6)	1117 (26.9)
Prescriber			
General practitioner	1752 (79.6)	913 (76.0)	2958 (71.3)
Pulmonologist	365 (16.6)	214 (17.8)	1026 (24.7)
Other specialist	84 (3.8)	74 (6.2)	162 (3.9)
Use of other respiratory drugs[a]			
Any drug	663 (30.1)	626 (52.1)	1500 (36.2)
SAMA	319 (14.5)	264 (22.0)	503 (12.1)
SABA	235 (10.7)	234 (19.5)	918 (22.1)
SABA-SAMA FDC	71 (3.2)	62 (5.2)	205 (4.9)
ICS	217 (9.9)	339 (28.2)	357 (8.6)
Xanthine derivatives	11 (0.5)	28 (2.3)	38 (0.9)
Leukotriene receptor antagonists	2 (0.1)	3 (0.2)	16 (0.4)
Use of co-medication related to COPD[a]			
Coughing agents	328 (14.9)	177 (14.7)	748 (18.0)
Mucolytics	237 (10.8)	132 (11.0)	408 (9.8)
Nasal preparations	135 (6.1)	61 (5.1)	270 (6.5)
Oral corticosteroids	455 (20.7)	335 (27.9)	1064 (25.7)
Oral antibiotics	1236 (56.2)	635 (52.9)	2485 (59.9)
Hospitalisation for COPD[b]	29 (1.3)	39 (3.2)	68 (1.6)
Co-morbidity[a]			
Number of different drug classes used besides respiratory drugs			
0–1 classes	207 (9.4)	133 (11.1)	445 (10.7)
2–3 classes	596 (27.1)	336 (28.0)	1116 (26.9)
4–5 classes	776 (35.3)	404 (33.6)	1401 (33.8)
≥6 classes	622 (28.3)	328 (27.3)	1184 (28.6)

LAMA, long-acting muscarinic antagonists; LABA, long-acting β2-agonists; FDC, fixed dose combinations; ICS, inhaled corticosteroids; SAMA, short-acting muscarinic antagonists; SABA, short-acting β2-agonists.

[a] Determined in the year before study entry date.

[b] Determined in the period from 1996 until study entry date.

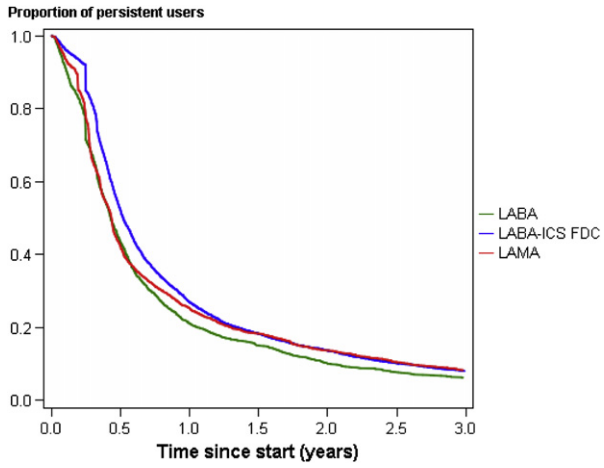

Figure 1 Kaplan Meier survival curve showing proportion of persistent users up to three years after start per type of initial long-acting inhaled monotherapy.

add-ons and 60% of 315 switches). Similar changes in treatment were observed in non-persistent patients with at least one year of follow-up (data not shown).

Including therapy changes, persistence rates with any long-acting inhaled drug at 1, 2 and 3 years after start were 36%, 23% and 17% respectively. For a subset of patients with a primary or secondary discharge diagnosis of COPD in their entire available history and follow-up ($n = 903$) these rates were 50%, 33% and 26%.

Classification of study patients based on treatment episodes of continuous use of any long-acting inhaled drug within three years of follow-up, resulted in 21% regular users, 34% inconsistent users and 28% short-term users (in addition to 17% persistent users as mentioned above). Table 3 shows the co-medication use for these different types of users. Short-term users had the lowest proportion of patients using oral corticosteroids or oral antibiotics (30% compared to 43—50% for corticosteroids, and 69% compared to 76—79% for antibiotics). Similarly, respiratory drugs besides long-acting drugs were less frequently used among short-term users (34% compared to 46—54%).

Discussion

In this population-based cohort study among COPD patients starting use of LAMA, LABA or LABA-ICS FDC, only 21—27% of patients were still receiving dispensings of their initial monotherapy after one year. Of patients who did not appear to continue with the initial monotherapy, 20—40% changed therapy (either add-on or switch). Including therapy changes, one year persistence with any long-acting inhaled drug was still only 36%. Two and three years after start these rates were 23% and 17%, respectively.

Selection of COPD patients for the current study was based on respiratory drug use, as also done by de Melo et al.[9] and in the previous PHARMO study.[6] By applying exclusion criteria, such as age <55 years at onset of respiratory drug use, prior use of asthma-specific drugs, and asthma hospitalisation, as many asthma patients as possible were excluded. Furthermore, patients with COPD-like symptoms because of e.g. lung cancer or lung fibrosis were excluded based on hospitalisations. However, we could not rule out that some patients treated for diseases other than COPD are included in the study cohort, e.g. patients who developed or re-developed asthma late in life. No information on smoking history, which would have helped confirm a diagnosis of COPD, was available. Therefore, we performed a sub-analysis in 903 patients with a hospitalisation with a primary or secondary discharge diagnosis of COPD in their entire available history and follow-up in PHARMO RLS. Although persistence was higher in this subset of certain COPD patients, rates were still low; only 50%, 33% and 26% of patients were still using any long-acting inhaled drug after 1, 2 and 3 years.

Long-acting bronchodilators are recommended when patients continue to experience symptoms on short-acting drugs. However, only one-third of our study patients had used SAMA, SABA or SABA-SAMA FDC in the year before start of LAMA, LABA or LABA-ICS FDC use. A post-hoc analysis revealed that in this subset of patients persistence was also low: 45%, 30% and 22% of patients were still using any long-acting inhaled drug at 1, 2 and 3 years after start.

Persistence was based on permissible gaps between dispensings of 60 days or less. Using a larger gap would have yielded higher persistence rates. A post-hoc analysis revealed that even when allowing 90-day gaps only 47% of patients were still using any long-acting inhaled drug after one year. Two and three years after start these rates were 31% and 24%, respectively.

To our knowledge, this is one of the first daily practice-based studies on persistence with any long-acting inhaled COPD drug. Available information in the literature is restricted to persistence with the initial long-acting inhaled COPD drug.[6,7] The proportions of new LABA and LABA-ICS FDC users still using this monotherapy after one year as observed in our study (i.e. 21% and 27%) are slightly higher than reported by Breekveldt-Postma et al. (13% and 17%,[6]) and Cramer et al. (around 16% and 12%,[7]). However, we only included patients with at least a second dispensing for

Table 2 First therapy change of COPD patients who were non-persistent with the initial long-acting inhaled monotherapy after one year of follow-up.

Initial drug	non-persistent patients, *N*	First therapy change			
		add-on, *n* (%)	switch, *n* (%)	restart, *n* (%)	stop, *n* (%)
LAMA	1643	240 (14.6)	206 (12.5)	223 (13.6)	974 (59.3)
LABA	947	83 (8.8)	296 (31.3)	194 (20.5)	374 (39.5)
LABA-ICS FDC	3027	335 (11.1)	315 (10.4)	873 (28.8)	1504 (49.7)

Table 3 Use of oral corticosteroids, oral antibiotics and respiratory drugs besides long-acting drugs within three years of follow-up stratified by type of user of long-acting drugs.

	Type of user of long-acting drugs			
	Short-term users $N = 2110$, n (%)	Inconsistent users $N = 2567$, n (%)	Regular users $N = 1612$, n (%)	Persistent users $N = 1259$, n (%)
Oral corticosteroids	638 (30.2)	1099 (42.8)	756 (46.9)	627 (49.8)
Oral antibiotics	1461 (69.2)	2025 (78.9)	1235 (76.6)	950 (75.5)
Respiratory drugs besides long-acting drugs				
Any drug	718 (34.0)	1169 (45.5)	846 (52.5)	680 (54.0)
SAMA	240 (11.4)	354 (13.8)	292 (18.1)	236 (18.7)
SABA	306 (14.5)	593 (23.1)	417 (25.9)	341 (27.1)
SABA-SAMA FDC	88 (4.2)	158 (6.2)	119 (7.4)	96 (7.6)
ICS	293 (13.9)	458 (17.8)	308 (19.1)	255 (20.3)
Xanthine derivatives	26 (1.2)	44 (1.7)	51 (3.2)	45 (3.6)
Leukotriene receptor antagonists	15 (0.7)	76 (3.0)	54 (3.3)	26 (2.1)

any of the long-acting inhaled drugs within 180 days after study entry. Furthermore, study periods, patients' age and/or persistence measurements differed. Our one-year persistence rate for LAMA alone (i.e. 25%) was similar to Cramer's rate (27%) but lower than found by Breekveldt-Postma et al. (37%). The latter high persistence rate is likely to be the result of tiotropium being prescribed to a selected group of patients shortly after its market introduction. Compared to our study patients, study patients from Breekveldt-Postma et al. more often received their first prescription from a pulmonologist, had a hospitalisation for COPD in the year prior to start of tiotropium use and used co-medication related to COPD. These factors may be indicative of a higher disease severity, which has been shown to be associated with increased persistence.[10]

In addition to the above mentioned persistence studies, there are studies on refill adherence and medication possession ratios, including long- as well as short-acting inhaled drugs.[11,12] Furthermore, studies specifically focusing on persistence with ICS have been performed.[10,13] These studies all also show that adherence to asthma/COPD drugs in general is low.

A major strength of our study is that we estimated persistence with the initial therapy as well as with any long-acting inhaled drug for COPD. Furthermore, in addition to the dichotomous outcome 'persistent', study patients were classified into four user types based on their pattern of use of long-acting inhaled drugs within three years of follow-up. This analysis showed that 55% of patients, although not persistent for three years, resumed long-acting drug use after a gap of at least 61 days (i.e. the 4179 regular and inconsistent users). This may indicate that symptom control was insufficient without using long-acting drugs or be related to seasonal or infrequent symptoms. A post-hoc analysis revealed that the majority of these patients most likely had not used any respiratory drugs during the gap in long-acting drug use: only 39% of patients had a dispensing of other respiratory drugs in the 90 days before or after the stop date.

From the user type classification we also know that 28% of patients only had long-acting inhaled drug dispensings in the first year after start (i.e. the 2110 short-term users). Based on the information on use of SAMA, SABA, SABA-SAMA FDC, ICS, xanthine derivatives, leukotriene receptor antagonists, oral corticosteroids and oral antibiotics within three years of follow-up, these patients seem to have had less severe disease and may have had sufficient symptom control on short-acting drugs only. However, from the post-hoc analysis we know that among short-term users only 27% had a dispensing of other respiratory drugs in the 90 days before or after the stop date.

Poor adherence to treatment in daily practice is likely to limit optimal disease management, as shown for e.g. antihypertensives, antidiabetics, statins and bisphosphonates.[14–17] Future studies from daily practice should determine the impact of poor persistence with COPD drugs on patients' outcomes such as lung function and rate of exacerbations. In such a study accurate information on severity of COPD is necessary as this is likely to be associated with persistence as well as with the patient's outcome; low persisters may be the mild COPD patients who have better short-term outcomes.

To improve persistence with long-acting inhaled drugs, an understanding of (patients') reasons to (temporarily) stop the use of these drugs is critical. Reasons for poor persistence mentioned by patients in a questionnaire study included difficulty in handling the inhaler, confusion about the medications, or simply because the patient was feeling good.[3,18] With this information health professionals can undertake activities to help their patients receive the most appropriate treatment and continue taking it. In addition, via targeted information and continuing-education measures the medical care of COPD patients may be improved.[3–5]

In conclusion, this analysis of dispensings indicates that persistence with the initial long-acting inhaled drug in COPD is low, with a substantial proportion of patients changing therapy. Even when those who switch or add-on therapy are considered persistent, rates remain low. Whether these changes in dispensing patterns are physician-instigated or patient-driven cannot be determined from these data. Neither do we know the factors driving the changes e.g. poor efficacy, adverse events, dosing regimen, device acceptability etc. However, the fact that persistence is low indicates that the currently available first-line maintenance treatments may not be adequate and/or that management of

patients is suboptimal. Future research should determine the factors impacting on persistence and the impact of poor persistence with COPD drugs on symptom relief and clinical outcomes.

Conflict of interest statement

This study was financially supported by an unrestricted grant from Novartis Horsham Research Centre, West Sussex, United Kingdom. No limitations were set with regard to the conduct of the study and the writing of the manuscript. Fernie Penning-van Beest, Myrthe van Herk-Sukel and Ron Herings are employees of the PHARMO Institute, which receives grants from several pharmaceutical companies, including Novartis. Rupert Gale is an employee of Novartis.

Acknowledgements

We would like to thank S. van der Bij for her work in the conduct of the study.

References

1. Chronic Obstructive Pulmonary Disease (COPD). Fact sheet No 315 [online]. [accessed 19.06.09], http://www.who.int/mediacentre/factsheets/fs315/en/index.html; May 2008.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD [online]. [accessed 19.06.09], http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989; 2008.
3. Restrepo RD, Alvarez MT, Wittnebel LD, Sorenson H, Wettstein R, Vines DL, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis* 2008;**3**(3):371—84.
4. Foster JA, Yawn BP, Maziar A, Jenkins T, Rennard SI, Casebeer L. Enhancing COPD management in primary care settings. *Med Gen Med* 2007;**9**(3):24.
5. Glaab T, Banik N, Rutschmann OT, Wencker M. National survey of guideline-compliant COPD management among pneumologists and primary care physicians. *Int J Chron Obstruct Pulmon Dis* 2006 Aug;**3**(3):141—8.
6. Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers JW, Herings RM. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. *Respir Med* 2007 Jul;**101**(7):1398—405.
7. Cramer JA, Bradley-Kennedy C, Scalera A. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. *Can Respir J* 2007 Jan—Feb;**14**(1):25—9.
8. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health* 2000;**3**(6):417—26.
9. de Melo MN, Ernst P, Suissa S. Inhaled corticosteroids and the risk of a first exacerbation in COPD patients. *Eur Respir J* 2004 May;**23**(5):692—7.
10. Breekveldt-Postma NS, Gerrits CM, Lammers JW, Raaijmakers JA, Herings RM. Persistence with inhaled corticosteroid therapy in daily practice. *Respir Med* 2004 Aug;**98**(8):752—9.
11. Haupt D, Krigsman K, Nilsson JL. Medication persistence among patients with asthma/COPD drugs. *Pharm World Sci* 2008 Oct;**30**(5):509—14.
12. Krigsman K, Moen J, Nilsson JL, Ring L. Refill adherence by the elderly for asthma/chronic obstructive pulmonary disease drugs dispensed over a 10-year period. *J Clin Pharm Ther* 2007 Dec;**32**(6):603—11.
13. Blais L, Bourbeau J, Sheehy O, LeLorier J. Inhaled corticosteroids in COPD: determinants of use and trends in patient persistence with treatment. *Can Respir J* 2004 Jan—Feb;**11**(1):27—32.
14. Breekveldt-Postma NS, Penning-van Beest FJ, Siiskonen SJ, Koerselman J, Klungel OH, Falvey H, et al. Effect of persistent use of antihypertensives on blood pressure goal attainment. *Curr Med Res Opin* 2008 Apr;**24**(4):1025—31.
15. Penning-van Beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. *Eur Heart J* 2007 Jan;**28**(2):154—9.
16. Penning-van Beest FJA, van der Bij S, Erkens JA, Kessabi S, Groot M, Herings RM. Effect on non-persistent use of oral glucose-lowering drugs on HbA1c goal attainment. *Curr Med Res Opin* 2008 July;**24**(9):2523—9.
17. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med* 2009 Feb;**122**(Suppl. 2):S3—13.
18. George J, Kong DC, Thoman R, Stewart K. Factors associated with medication nonadherence in patients with COPD. *Chest* 2005 Nov;**128**(5):3198—204.