

## ORIGINAL ARTICLE

# The use of inhaled corticosteroids in the United Kingdom and the Netherlands

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**Abstract** This study examined the utilisation patterns of inhaled corticosteroids in England/Wales and the Netherlands. Computerised medical records from the GPRD (U. K.) and PHARMO (the Netherlands) databases were used. It included 284 733 English/Welsh and 27 761 Dutch adult patients who were prescribed inhaled corticosteroids during the 10-year study period. Our results showed that, in both study populations, overall use of inhaled corticosteroids increased over the period studied, with its prevalence rising steeply with age and declining in extreme old age. Decreased use of bronchodilators and oral corticosteroids in the early treatment of asthma was noted in our findings. In addition, a trend towards the decreasing use of oral corticosteroids concomitant with inhaled corticosteroid therapy was also observed for both groups. Our study found that only 42.1% of the GPRD and 31.1% of the PHARMO patients received a repeat prescription within the expected duration of the preceding inhaled corticosteroid prescription. In conclusion, our study found many similarities in the prescribing and use of inhaled corticosteroids between the two study populations. The observation of irregular use of inhaled corticosteroid among a substantial number of patients highlights a need for further study into the reasons for irregular use and its consequences on the effectiveness of treatment.

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doi: 10.1053/rmed.2002.1453, available online at <http://www.sciencedirect.com>

**Keywords** inhaled corticosteroids; utilization.

## INTRODUCTION

Inhaled corticosteroids are the most potent anti-inflammatory agents for treating asthma and act in a relatively non-specific manner by inhibiting a variety of inflammatory cells, cytokine expression, and transcription factors (1). Their use, initially restricted to patients with severe asthma, has recently been extended to include patients with less severe asthma after randomised clinical trials demonstrated the efficacy of inhaled corticosteroids in patients with milder forms of asthma (2). It has now been

proposed that inhaled corticosteroids should be considered as first-line drugs in asthma prophylaxis for all but the mildest cases. Current U.K. guidelines outlined by the British Thoracic Society advise starting treatment with occasional use of  $\beta$ -agonists. If the asthma remains poorly controlled and there is an increased requirement for  $\beta$ -agonists more than once daily, then regular daily use of inhaled corticosteroids is recommended (3). The role of inhaled corticosteroids is that of maintenance therapy to prevent asthma exacerbations (1). For acute, severe, or rapidly deteriorating, asthma, a short course of an oral corticosteroid is indicated, combined with the daily use of inhaled corticosteroids (3).

The objective of this study was to investigate utilisation patterns and extent of regular use of inhaled corticosteroids, as well as their impact on oral corticosteroid

Received 8 april 2002, accepted in revised form 4 September 2002

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use, in two large patient samples, one in the U. K. and the other from the Netherlands. Information was obtained from the General Practice Research Database (GPRD) that contains the computerised medical records of a large group of medical practices in England and Wales (4), and from the PHARMO database that links community pharmacy and hospital data from several regions of the Netherlands (5). Both databases have been widely used in epidemiological drug research (6–10).

## METHODS

### Databases

#### *England and Wales*

The data for England and Wales were obtained from the GPRD, owned by the Department of Health and managed by the Medicines Control Agency in the U. K. (4). This database comprises the entire computerised medical records of a sample of general practitioners (GPs) in the country. GPs play a key role in the U. K. health-care system, as they are responsible for primary health care and specialist referrals. All members of the population are registered with a single practice, which centralises the medical information not only from the GPs but also from specialist referrals and hospital attendances. The current study included 683 practices currently incorporated in the GPRD and thereby comprised a 6% sample of the U. K. population. Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) and READ codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). The prescription information is cross-referenced to the British National Formulary (11). A comparison of GPRD with the Fourth Morbidity Survey in General Practice found that GPRD was a valid source of epidemiological information on respiratory disease (12).

#### *The Netherlands*

The PHARMO database contains the drug dispensing records from community pharmacies and the admission records from hospitals in a population of about 500 000 patients in the Netherlands (about 3% of the total population). The PHARMO database is confined to the complete population of 18 medium-sized cities in the Netherlands and collects prescriptions and hospital admission records of residents. The drug dispensing and hospital admission histories are linked on an individual basis using probability methods (5). The database contains information on the use of prescription medication, hospital discharge diagnoses (ICD-9), and operations or procedures that were performed in the hospital. The prescription information is cross-referenced to the ATC classification (13).

### Study population and methods

The two study cohorts consisted of all adult patients (18 years or older) who received one or more prescriptions for inhaled corticosteroids during the period of time of study data collection (January 1987–December 1997 for GPRD and January 1987–December 1998 for PHARMO). The cohort entry date for each inhaled corticosteroid taker was defined as the date of the first inhaled corticosteroid prescription after enrolment in PHARMO or GPRD. Patients were censored at the time of death, end of study period, or, for GPRD, patient's change of practice. Dividing the total duration of inhaled corticosteroid use by the total observation time of GPRD made a point prevalence estimate for inhaled corticosteroid use. The total observation time was the cumulative number of patients registered in the database at 1 July of each calendar year. The duration of each prescription was based on the median recorded duration of use (28 days in GPRD and 40 days in PHARMO). This prevalence estimate provided a cross-sectional measure of inhaled corticosteroid utilisation. The prevalence of inhaled corticosteroid use could not be estimated for PHARMO prior to 1991, as no denominator data were available. No prevalence estimates were made for GPRD prior to 1990 because of the small number of practices included at that time and for 1997 because data collection was stopped that year.

The use of oral corticosteroids in the year before and after start of inhaled corticosteroid therapy was measured. An analysis was done over calendar time (covering a 1-year period of therapy) and included only patients who started inhaled corticosteroid therapy at least 1-year after start of data collection. Kaplan–Meier survival analysis was conducted in order to estimate the proportion of people who received oral corticosteroids within the first year of inhaled corticosteroid treatment. Patients were followed from the first inhaled corticosteroid prescription until 3 months after the last prescription, or until date of censoring (whichever came first). The proportion of people who received an oral corticosteroid prescription in the year preceding the start of inhaled corticosteroid treatment was also estimated. Prior use of bronchodilators was also evaluated.

The regularity of inhaled corticosteroid treatment and the time between two consecutive prescriptions was examined. For each patient, we randomly selected an inhaled corticosteroid prescription. For the patients with use prior to this selected prescription, the percentage of patients who received a prescription in the 6 months before the selected inhaled corticosteroid prescription was estimated. Furthermore, it was determined whether the selected inhaled corticosteroid prescription was given within the expected duration of the previous prescription (based on the cumulative number of doses divided by the prescribed daily dose).

Patients starting PHARMO/GPRD data collection in the previous 6 months were excluded from the analysis.

For the GPRD population, the indication for inhaled corticosteroid treatment was obtained by reviewing the morbidity recorded at the date on which a new course of treatment was started. At the commencement of new drug treatment, the GPs are required to record the indication for treatment on the same date in the medical record. This analysis included patients who received their first inhaled corticosteroid prescription at least 1-year after start of data collection for that patient.

## RESULTS

There were 284 733 inhaled corticosteroid users identified in GPRD and 27 761 in PHARMO (Table I). The majority of users in both populations were women (55.3% in GPRD and 53.9% in PHARMO). The age distribution of inhaled corticosteroid users was comparable with median age of 48 years in GPRD and 49 years in PHARMO. There were substantive differences in the application form of the inhaled corticosteroid. In England and Wales, inhaled corticosteroids were administered mostly by a pressurised metered dose inhaled (pMDI) (73.2% of all prescriptions) while in the Netherlands, dry powder ad-

ministration was considerably more popular (83.0% of all prescriptions). The distribution of prescribed daily dose was comparable between the populations: 44.6% of the GPRD patients were prescribed a daily dose of 400 µg beclomethasone equivalent or less compared to 46.8% of the PHARMO patients.

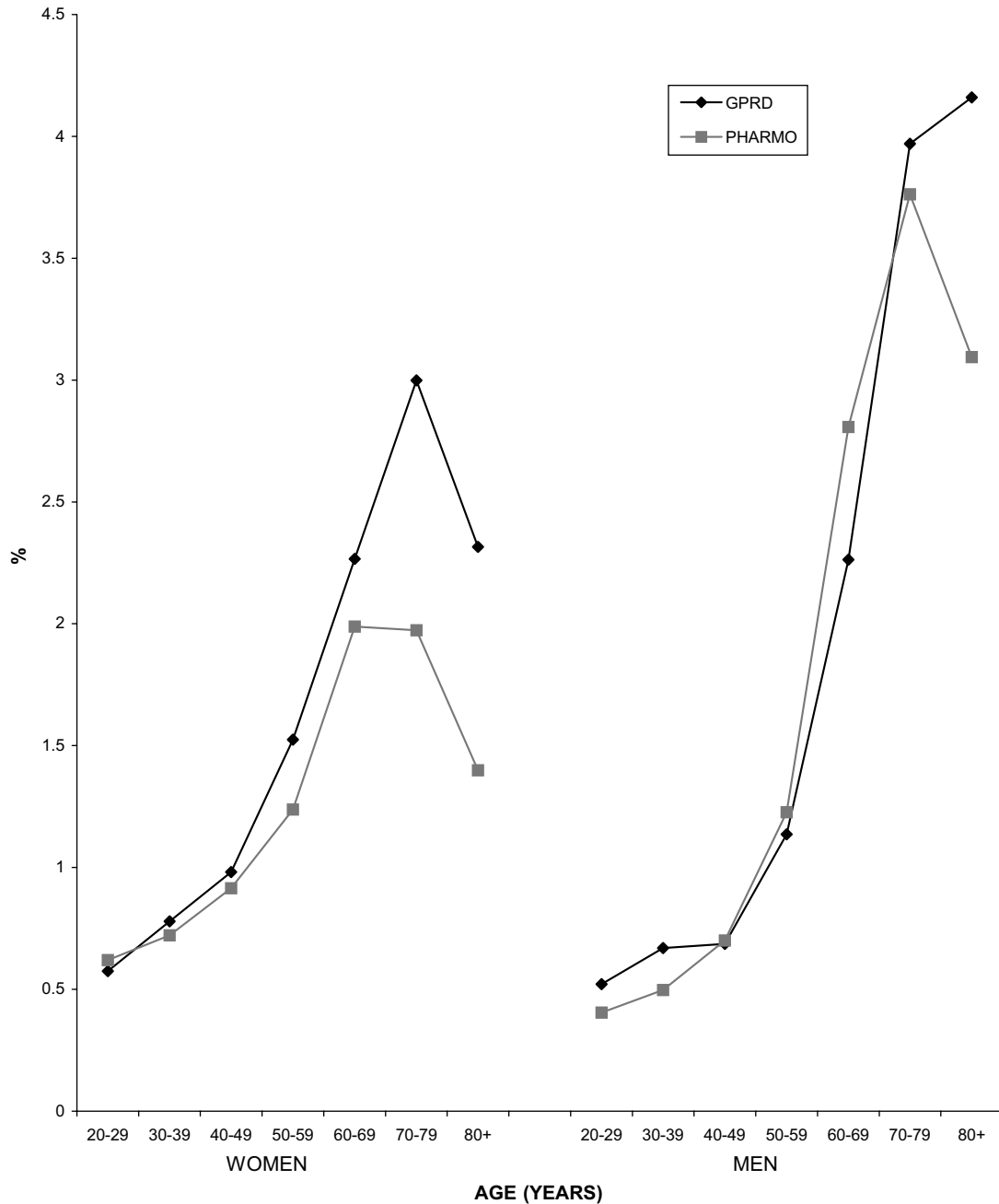
Figure 1 shows the use of inhaled corticosteroids in England/Wales and the Netherlands. It was found that the prevalence of use rises steeply with age in both populations, with a tendency towards lower use in extreme old age. In GPRD, women used inhaled corticosteroids more frequently than men up to the age of 70 years, with more frequent use among men after this age. A similar pattern was seen in PHARMO, with the reversal in the sex ratio of use taking place at 60 years of age. Use of inhaled corticosteroids was greater in England/Wales compared with the Netherlands: 1.4% in GPRD and 1.1% in PHARMO. Use of inhaled corticosteroids increased significantly over calendar time (Table 2). In GPRD, 1.1% of adult population used inhaled corticosteroids in 1991 compared to 1.7% in 1996. For PHARMO, these figures were 0.8 and 1.4%, respectively.

In the analysis of the prescribing patterns and regularity of use, it was found that 80.5% of the GPRD patients and 76.6% of the PHARMO patients with prior use had received a prescription for inhaled corticosteroids in

**TABLE I.** Characteristics of inhaled corticosteroid users

	GPRD	PHARMO
Total number of users	284 733	27 761
Number of women	157 561 (55.3%)	14 955 (53.9%)
Age (year)		
Mean	48.5	49.6
Median	48	49
Follow-up per person (year)		
Mean	2.8	4.2
Medium	2.4	3.6
Total number of inhaled prescriptions	3 322 210	2 575 78
Application form		
pMDI	73.2%	16.3%
Dry powder	25.8%	83.0%
Nebuliser	1.0%	0.6%
Type of inhaled corticosteroids		
Beclomethasone dipropionate	81.4%	63.6%
Budesonide	13.8%	23.4%
Fluticasone propionate	4.7%	13.0%
Daily dose (µg beclomethasone equivalent) <sup>a</sup>		
1–400	44.6%	46.8%
401–800	27.4%	36.0%
801–1500	16.0%	11.3%
1500 <sup>+</sup>	12.0%	5.9%

<sup>a</sup>Daily dose was missing in 6.0% of the PHARMO and 18.4% of the GPRD prescriptions.



**FIG. 1.** Prevalence of use of inhaled corticosteroid stratified by age and sex.

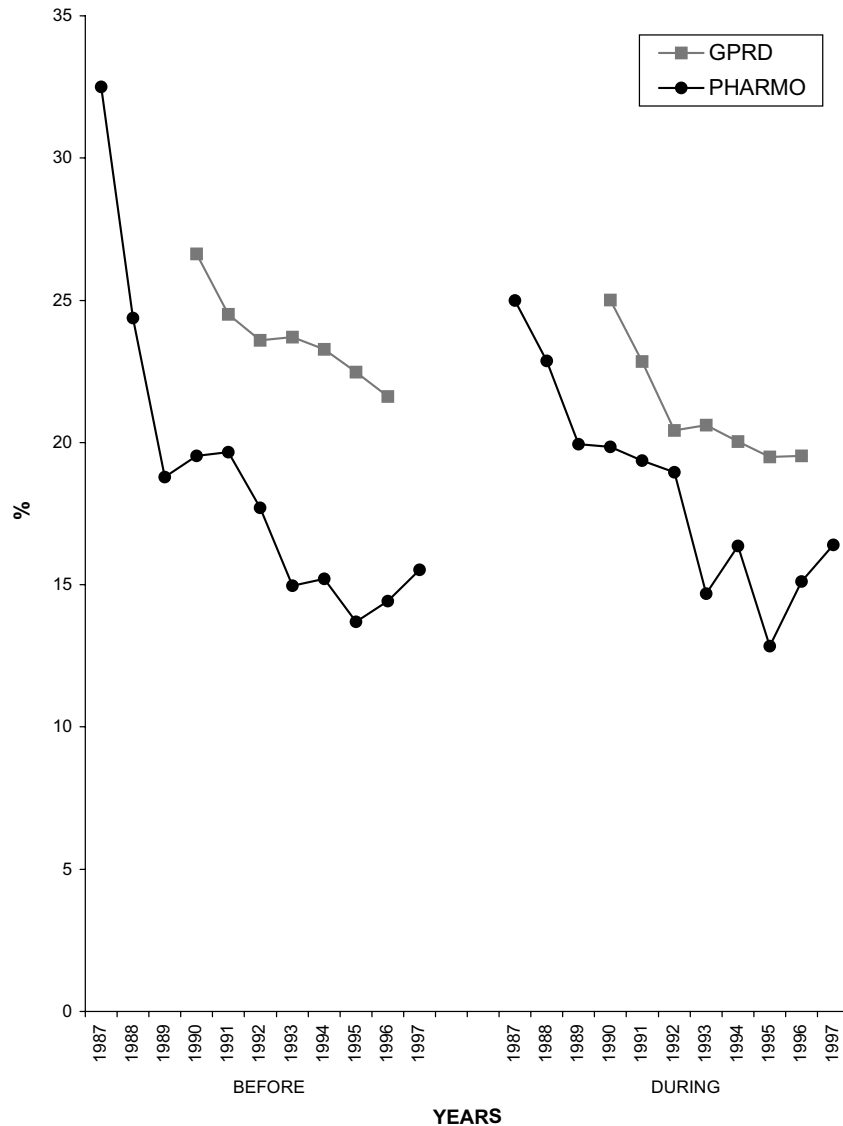
the 6 months before the selected prescription (Table 2). Taking into account the expected duration of inhaled corticosteroid treatment, 42.1% of the GPRD and 31.1% of the PHARMO patients received this repeat prescription within the expected duration of the preceding inhaled corticosteroid prescription. Elderly patients were more likely to receive repeat prescriptions within the period of duration of use: 50.7% of the GPRD patients and 41.2% of the PHARMO patients aged 75 years or older, compared to 34.0% of the GPRD patients and 24.7% of the PHARMO patients younger to 45 years.

Table 3 follows the changes in the use of inhaled corticosteroid treatment over the calendar time 1987–1997. It shows that the proportion of women and age of patients starting treatment did not vary substantially over calendar time. In 1990, the average age of the user was 50 years in GPRD and 56.2% were women, compared to an average age of 50 years and 57.9% women in 1996. In PHARMO, the average ages were 50 and 49 and the proportion of women 54.6 and 55.5%, respectively. There was a decrease over calendar time in the proportion of patients who started inhaled corticosteroid treatment

**TABLE 2.** Regularity of inhaled corticosteroid treatment

	GPRD		PHARMO	
	Rx in previous 6 months <sup>a</sup> (%)	Repeat Rx within treatment period <sup>a</sup> (%)	Rx in previous 6 months <sup>a</sup> (%)	Repeat Rx within treatment period <sup>a</sup> (%)
Overall	80.5	42.1	76.6	31.1
Sex				
Women	79.7	41.0	74.5	29.7
Men	81.4	43.5	78.9	32.6
Age (year)				
18–44	70.8	34.0	68.4	24.7
45–59	81.5	42.1	75.3	29.3
60–74	88.8	49.3	82.0	35.0
75+	89.6	50.7	87.6	41.2

<sup>a</sup>For patients who previously received another inhaled corticosteroid prescription.



**FIG. 2.** Use of oral corticosteroid before and during inhaled corticosteroid treatment.

**TABLE 3.** Changes in the utilisation of inhaled corticosteroids over calendar time

	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
<b>GPRD</b>											
Proportion of use	—	—	—	0.9%	1.1%	1.2%	1.4%	1.5%	1.6%	1.7%	—
Proportion of women <sup>a</sup>	—	—	—	56.2%	55.5%	55.1%	56.8%	58.8%	57.9%	57.9%	—
Average age (years) <sup>a</sup>	—	—	—	50.8	48.9	49.4	49.5	49.8	49.9	50.3	—
Proportion with use of bronchodilators year before <sup>a</sup>	—	—	—	68.4%	67.4%	64.4%	64.4%	62.3%	59.7%	56.0%	—
<b>PHARMO</b>											
Proportion of use	—	—	—	—	0.8%	0.9%	1.1%	1.3%	1.4%	1.4%	1.6%
Proportion of women <sup>a</sup>	51.9%	54.2%	56.1%	54.6%	54.1%	54.3%	52.7%	56.1%	55.6%	55.5%	58.0%
Average age (years) <sup>a</sup>	52.7	51.4	50.6	50.1	51.1	51.1	50.6	49.4	48.6	49.2	47.8
Proportion with use of bronchodilators year before <sup>a</sup>	78.8%	79.2%	73.4%	69.4%	64.9%	62.0%	56.8%	56.0%	52.6%	56.7%	56.5%

<sup>a</sup>In patients who started inhaled corticosteroid treatment at least 1 year after start of data collection.

after first using bronchodilators. This proportion decreased by 12% from 1990 to 1996 in both populations.

There was a trend over calendar time towards oral corticosteroids being used less frequently during inhaled corticosteroid therapy (Fig. 2). In 1990, 25.0% of the inhaled corticosteroid users in GPRD were prescribed an oral corticosteroid during the first year of inhaled corticosteroid therapy as compared to 19.5% in 1996. In PHARMO, this percentage of concomitant use of oral corticosteroids decreased from 19.9% in 1990 to 15.1% in 1996. Oral corticosteroids were also used less frequently over time in the year preceding the start of the inhaled corticosteroid therapy.

Of the GPRD patients who started inhaled corticosteroid treatment at least 1 year after start of data collection, asthma was the most frequently reported indication for treatment. Less frequent indications included bronchitis and other obstructive pulmonary disease. In the patients aged less than 45 years, 96.6% of the recorded respiratory morbidity concerned asthma and 3.4% bronchitis or other obstructive pulmonary disease. For patients aged 75 years or older, these figures were 49.9 and 50.1%, respectively. No information on the indication for treatment was available for the PHARMO patients.

## DISCUSSION

This study examined the utilisation patterns of inhaled corticosteroids of two large populations in two countries. The elderly in particular were found to use inhaled corticosteroids frequently. In both study populations, England/Wales and the Netherlands, inhaled corticosteroid use has increased substantially over time. Inhaled corticosteroid treatment was initiated more frequently over calendar time without prior use of bronchodilators and its concomitant use with oral corticosteroids showed a decline over calendar time in both populations.

The results also show that, in both populations, a substantial proportion of patients were not using inhaled corticosteroids continuously. Our findings suggest that younger patients, in particular, were more likely to use inhaled corticosteroids for symptomatic treatment than regular treatment. The maximum beneficial effect of inhaled corticosteroids may take from 1 to 3 months to achieve (14). Thus, a possible reason for irregular use by patients may be that this slow onset of the drug's effectiveness does not convince patients that inhaled corticosteroids are contributing to the asthma control. A study evaluating compliance to asthma drugs found that it was significantly lower in patients using inhaled corticosteroids compared to those using theophylline. The difference was partly attributed to the perception of immediate beneficial effects of theophylline (15). This explanation is supported by the findings of a case-control

study of patients hospitalised for an asthma exacerbation. It found that cases expressed less interest in optimal usage of inhaled corticosteroids and more confidence in bronchodilators (16). Our results are in line with a cross-sectional review of asthma treatment in five general practices in England. Among the patients using inhaled corticosteroids, only 35% received this treatment regularly (17).

There are data to suggest that regular use of inhaled corticosteroids provides a better overall control of asthma compared to symptomatic use. In epidemiological studies, regular use of inhaled corticosteroids was associated with a decreased risk of death from asthma (18,19). It was also reported that sporadic use of inhaled corticosteroids could be associated with higher rates of death from asthma (18). Use of inhaled corticosteroids in acute asthma exacerbations may also be less effective. A randomised double-blind study in children with a severe asthma exacerbation found that the degree of improvement in pulmonary function in the initial 4 h among those treated with an oral corticosteroid was about twice that in those given an inhaled corticosteroid. A possible reason for this finding may be suboptimal delivery of inhaled corticosteroids into the lung in case of severe airway narrowing (20). Further research is needed to assess the effectiveness of irregular use of inhaled corticosteroids.

The increase in the use of inhaled corticosteroids shown in this study is consistent with previously reported findings (21). Over a 7-year period, inhaled corticosteroid use almost doubled in both England/Wales and the Netherlands. One possible explanation may be an increased prevalence of asthma. There have been a number of epidemiological studies repeated in more or less the same population with the same or similar methods, which found that the asthma prevalence and severity have increased (22). The increased utilisation may also be explained, partly, by changing prescription practices in the treatment of asthma. In both England/Wales and the Netherlands, prior use of bronchodilators has decreased over time. At the end of the study, almost half of the patients started inhaled corticosteroid treatment without recent prior use of bronchodilators. Similarly, use of oral corticosteroids also decreased, along with its use prior to, and during, inhaled corticosteroid treatment.

A surprising finding in this study was that in both populations a substantive proportion of patients was not treated with bronchodilators prior to starting inhaled corticosteroids. One possible explanation for this may be that asthma treatment (i.e., bronchodilators) was started in the hospital and not recorded in our databases. However, we measured use of bronchodilators over a period of 1 year and any long-term treatment is likely to be recorded in our databases. In the U.K. treatment that is started in the hospital is generally continued

by the GP. Another possible explanation for this finding is the variation in the treatment patterns in general clinical practice. A recent study in six general practices in England found that 58% of the asthma patients used treatment regimens that were not consistent with treatment guidelines. The reasons for this inappropriate medication use resulted mostly of underuse of inhaled corticosteroids in the setting of regular bronchodilator use (23). Further research is needed to better understand the reasons for underuse of bronchodilators in patients using inhaled corticosteroids.

Information for this study was derived from prescription information. This approach has limitations: the actual amounts of drugs taken by patients could not be assessed. Patients may not have taken the drug or have taken it at different dose and duration than that prescribed by the physician. Nevertheless, large gaps between refill prescriptions may suggest some problems with compliance and regularity of use. In GPRD, the GP dose instructions were not collected systematically. It was recorded because the text had to be coded by the researchers. In both populations, possible instructions of dose reductions in case of better asthma control were not recorded.

In conclusion, inhaled corticosteroids are frequently being used in England/Wales and the Netherlands, and their usage has almost doubled over the period covered by our study. Our results indicate irregular use of inhaled corticosteroid among a substantial number of patients, highlighting a need for further studies to elucidate the reasons for irregular use and the effectiveness of inhaled corticosteroids with irregular use.

## Acknowledgements

We thank EPIC, the GPRD license holder, for their support. The GPRD data in this study were obtained from another study that was funded by Procter & Gamble Pharmaceuticals.

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