The predictive value of asthma medications to identify individuals with asthma — a study in German general practices

Wolfgang Himmel, Eva Hummers-Pradier, Holger Schümann and Michael M Kochen

SUMMARY

Background: *The assessment of prescribing performance by aggregated measures mainly developed from automated databases is often helpful for general practitioners. For asthma treatment, the frequently applied ratio of anti-inflammatory to bronchodilator drugs may, however, be misleading if the specificity of a drug for the treatment of asthma, compared with other diseases, is unknown.*

Aim: *To test the association of specific drugs with the diagnosis of asthma compared with other diagnoses.*

Design of study: *Cross-sectional study analysing prescription data from a retrospective chart review.*

Setting: *Eight general practices and one community respiratory practice in a town in Northern Germany.*

Method: *All patients in the participating practices who received at least one of the 50 asthma drugs most frequently prescribed in Germany within the past 12 weeks were identified. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to reveal any association between a specific drug and the diagnosis of asthma. The unit of analysis was the item prescribed.*

Results: *Topical betamimetics (e.g. salbutamol, fenoterol) were the most often prescribed asthma drugs in the general practices (52.1%) and in the respiratory practice (57.6%). Inhaled steroids accounted for 15% and 13%; systemic steroids accounted for 10% and 13%, respectively. In the general practices, inhaled betamimetics had a moderate marker function for asthma (OR = 2.0; 95% CI = 1.14–3.58). A fixed oral combination drug of clenbuterol plus ambroxol was a marker drug against asthma (OR = 0.35; 95% CI = 0.20–0.61). In the respiratory practice, the diagnosis of asthma was strongly marked by fixed combinations of cromoglycate plus betamimetics (OR = 29.0; 95% CI = 6.86–122.24) and moderately by inhaled betamimetics (OR = 2.6; 95% CI = 1.28–5.14). In contrast, systemic steroids (OR = 0.24; 95% CI = 0.10–0.57) and even inhaled steroids (OR = 0.46; 95% CI = 0.22–0.96) proved to contradict the diagnosis of asthma.*

Conclusion: *Only betamimetics were markers for asthma patients in both types of practices; inhaled steroids, however, were not. Combinations of cromoglycate were markers in the respiratory practice only. Limited specificity of drugs for a disease (e.g. asthma) should be taken into account when analysing prescribing data that are not diagnosis linked.*

Keywords: *pharmacoepidemiology; drug prescriptions; asthma, general practice.*

W Himmel, PhD, sociologist, E Hummers-Pradier, MD, research fellow, H Schümann, MD, registrar, and M M Kochen, MD, MPH, PhD, FRCGP, professor of general practice, Department of General Practice, University of Göttingen, Germany.

Address for correspondence

Dr Wolfgang Himmel, Department of General Practice, University of Göttingen, Humboldtallee 38, 37073 Göttingen, Germany.
E-mail: whimmel@gwdg.de
Submitted: 2 October 2000; Editor's response: 17 January 2001; final acceptance: 1 June 2001.

Introduction

ATTEMPTS to evaluate the quality of prescribing performance in the past have sometimes used algorithms or aggregated measures as prescribing indicators, mainly developed from prescription databases (e.g. pharmacy records or data from sickness funds). These databases frequently do not include diagnoses. The subsequent assumption is that a patient's disease can be identified with sufficient confidence through the drugs he or she receives. In the case of asthma patients, for example, the percentage of corticosteroids or the ratio of inhaled corticosteroids to bronchodilator drugs are frequently used as aggregated indicators of the quality of drug treatment.[1-4] However, as long as anti-asthmatic medications are not linked to diagnoses and as long as the degree to which asthma drugs identify asthma patients is unknown, conclusions from prescribing data may be misleading.

The aim of this study was to determine the correlation between certain drugs and the diagnosis of asthma compared with other diagnoses (known as the predictive value, or marker function of a drug). We compared the marker function of anti-asthmatic drugs prescribed by general practitioners (GPs) with a respiratory practice's prescriptions. In this study, only the reliability of prescribing indicators derived from automated databases was studied and not the quality of asthma prescriptions in ambulatory practices. This would have required a patient-based analysis.

Method

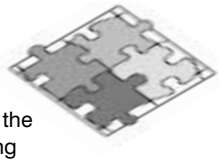
Study design

In this cross-sectional study, prescription data from a retrospective chart review were analysed and the diagnoses as documented in the patient chart were determined for each prescription of an asthma drug. The unit of analysis was the item prescribed, as the predictive value of an individual prescription for a patient's diagnosis was to be studied.

Research setting

All computerised general practices and the only community respiratory physician in a medium-sized town in the North of Germany were asked to participate in the study. In Germany, asthma (and chronic obstructive pulmonary disease [COPD]) patients are usually managed by both general practitioners and respiratory physicians with mutual referrals. Of the 30 general practices, 16 were willing to take part in the study. Because of technical problems (compatibility of the practice software), only eight practices (six of them single-handed, two with two partners) could be enrolled. The respiratory physician also took part in the study. The town has

HOW THIS FITS IN



What do we know?

Use of aggregated prescription data is widely recommended (for example, by the British Audit Commission) for calculating prescribing indicators to assess the quality of physicians' prescribing. Several studies using prescribing indicators, such as the ratio of inhaled corticosteroids to bronchodilator drugs, revealed shortcomings in the pharmacotherapy of asthma in primary care. It is widely believed that asthma medications are a fairly good proxy for asthma prevalence, i.e. that they reliably identify patients with asthma.

What does this paper add?

Contrary to expectations, there were no drugs which reliably identified asthma patients in general practice. In a pulmonologist's practice, only one class of drugs — a combination of cromoglycate and betamimetics — was strongly associated with the diagnosis of asthma. Corticosteroids were very frequently prescribed for COPD and did not fulfil a marker function for asthma. The results of this study might serve as a note of caution to physicians, clinical pharmacologists and health managers as to the interpretation of prescribing data without diagnosis linkage as proxies for quality of care in chronic airflow diseases.

about 70 000 inhabitants with a catchment area of about 100 000 inhabitants.

Selection of subjects

First, the proprietary names of the 50 anti-asthmatic medications that were most frequently prescribed in Germany at the time of this study were listed according to the German Drug Prescription Report.[5] These 50 medications represent 93% of all anti-asthmatic drugs prescribed by ambulatory doctors (GPs and community specialists alike). The most frequently prescribed anti-asthmatic drugs were Berodual® (a topical preparation of ipratropium bromide plus fenoterol), Spasmo-Mucosolvan® (oral preparation of clenbuterol plus ambroxol), Berotec® (inhaled fenoterol) and Sultanol® (inhaled salbutamol), which represent nearly one-quarter of all prescriptions in this class.[3] In the case of systemic corticosteroids, which were compiled separately in the Report, the participating doctors were asked which of these drugs they typically prescribed for airway obstruction. We grouped the individual drugs prescribed into 10 classes (Table 2) according to the Anatomic Therapeutic Chemical (ATC) classification code.[6]

Using a statistical module implemented in the practice software, all patients who were prescribed one or several of these drugs within the 12-week study period were retrieved. Age, sex, and corresponding diagnoses for each of these patients were extracted as documented in their charts. With reference to the *International Classification of Diseases* (ICD 10), the diagnoses given in the patient chart were manually compiled into five main categories: asthma; COPD; asthma-like symptoms; acute respiratory tract infections; and 'other' (e.g. lung cancer).

Analysis

The predictive value of a drug for a diagnosis was assessed in two ways: First, the specificity of a drug class for asthma was calculated, which is expressed as the number of prescriptions for patients with asthma in relation to all prescriptions of this drug class. Second, the marker function of a drug class was calculated using 2 x 2 contingency tables and expressed as the ratio between the likelihood of predicting the diagnosis of asthma and the likelihood of having any other diagnosis. For these odds ratios (ORs), 95% confidence intervals were also calculated. If the confidence interval did not include the value 1.0 then the predictive value was considered significant. All analyses were performed using SAS, version 8.[7]

Results

During the study period, 942 prescriptions for asthma drugs were identified. These asthma drugs were prescribed to 632 patients: 203 patients from the community respiratory practice and 429 patients from eight general practices (range = 23–94 per practice). Table 1 compares age, sex, and diagnoses of these patients. Half of them (n = 309) were diagnosed as having asthma or asthma-like symptoms, 193 (33%) were diagnosed as having COPD. Twenty-five (6%) of the general practice patients and 17 patients in the respiratory practice were documented with both diagnoses of asthma and COPD. For calculating the marker function of drugs for the diagnosis of asthma, these 42 patients were labelled as asthmatics. For 34 patients, mostly from the general practices, no diagnosis was documented in the context of the actual prescription. Only 'chronic' diagnoses, often noted a long time previously, were to be found in the charts. According to this information, 10 patients had atopic diseases (e.g. hay fever), nine had respiratory tract infections, and four had dyspnea. For the remainder, no piece of information could be detected. Because of an obvious lack of quality in documentation, all 34 patients were excluded from further analyses.

Prescription of anti-asthmatic drugs

Betamimetics (drug classes I to V in Table 2), which included fixed combinations with ipratropium, cromoglycate or ambroxol, were the asthma drugs most often prescribed in the general practices (52.1%) and in the respiratory practice (57.6%). In contrast, inhaled steroids accounted for 15% and 13% of asthma drugs, while systemic steroids accounted for 10% and 13%, respectively (Table 2). The relative frequencies of prescriptions were rather similar in both types of practices. Only Spasmo-Mucosolvan® was far more often prescribed in general practices than in the respiratory practice.

Specifity of anti-asthmatic drugs for the diagnosis of asthma

Only cromoglycate plus betamimetics in fixed combinations (class IV), proved to be a highly specific drug class when prescribed by the community respiratory practice, as nearly all patients (45/47) who received a drug from this class were asthmatics (Table 2). In the general practices, inhaled betamimetics were frequently prescribed for asthma patients (80%). Interestingly, only two-thirds of the oral as

Table 1. Patient sample.

Characteristics	Patients in general practice (n = 429)	Patients in respiratory practice (n = 203)
Female (%)	45.2	54.2
Age (years)		
Median	46	54
Interquartile range	22–65	28–66
Diagnoses *n* (%)		
Asthma	181 (42.2)	91 (44.8)
Asthma and COPD	25 (5.8)	17 (8.4)
Asthma-like symptoms	37 (8.6)	–
COPD	101 (23.5)	92 (45.3)
Acute infections	44 (10.3)	1 (0.5)
Other	7 (1.6)	–
No information	32 (7.5)	2 (1.0)

well as inhaled corticosteroids were prescribed for these patients. In the respiratory practice, the percentage of these drugs for asthma patients was even less than 40%. Only a minor part of fixed combinations of clenbuterol plus ambroxol (class V), which are popular in Germany, were prescribed for asthma patients.

Marker function of anti-asthmatic drugs for asthma and COPD

As shown in Table 3, the only significant, though weak, marker for asthma patients in the eight general practices were inhaled betamimetics, with an OR of 2.0. The fixed combination of clenbuterol plus ambroxol (class V) proved to be a significant marker for patients not having asthma (OR = 0.34). The respiratory physician's prescriptions served somewhat better as markers: combinations of cromoglycate (class IV; OR = 28.97) and, to a lesser degree, inhaled betamimetics (OR = 2.57) were specific for asthma patients. Berodual® (fenoterol plus ipratropium) was a highly specific marker 'against' asthma (OR = 0.22). Systemic, as well as inhaled, corticosteroids identified patients with COPD.

Discussion

Only one drug class in our study — the fixed combination of cromoglycate plus betamimetics (class IV), recommended in Germany for treatment of asthma in the early stages[8] — was strongly associated with the diagnosis of asthma in the community respiratory practice. None of the other classes of asthma drugs identified asthma patients precisely, either in the general practices or in the specialist practice. Even inhaled steroids, which are strongly recommended as first-line therapy for asthma and are controversially discussed for COPD,[9,10] were not highly specific markers for asthma. This corresponds to a Dutch study using a general practice database of prescribing records: only 69% of patients receiving inhaled steroids had asthma.[11] In our study, this rate was 67% for patients in general practice and less than 40% for the respiratory physician's patients. These results may reflect (a) shortcomings in the quality of asthma treatment, (b) shortcomings in the doctors' diagnostic reliability, or (c) shortcomings in the quality of the suggested prescribing indicator.

Shortcomings in the quality of asthma treatment

Although most GPs seem to be aware of asthma guidelines and recommendations,[12,13] several studies have shown that some patients with asthma remain poorly controlled, mostly because of an over-reliance on betamimetics and an under-use of corticosteroids.[14-16] In a cross-sectional study in six British general practices,[17] 58% of asthma patients used drug regimens that were not consistent with the national guidelines. Most patients inhaled betamimetics regularly without taking inhaled steroids (or taking them at a low dose). Patients and doctors alike may be sceptical towards corticostoids as a prophylactic treatment and prefer bronchodilators because they provide quick relief.[18,19] In this case, a low ratio of inhaled steroids to bronchodilators would indeed mirror deficits in asthma treatment.

Shortcomings in the doctor's diagnostic reliability

Many patients in general practice settings may not have a definite diagnosis and will sometimes be treated on a trial-and-error basis. This is reflected in the diagnostic category of asthma-like symptoms which in our study applied to nearly 9% of patients in the general practices but to no-one in the respiratory practice. This 9% may indicate a larger patient population with uncertain diagnoses. A Swedish study in primary care that re-examined patients with a diagnosis of asthma in their medical register found that half of these patients had COPD and suggests that about every third 'asthmatic' had been given the wrong diagnosis.[20] In our retrospective study, there was no possibility to check the validity of the diagnoses. The same holds true for any study based on automated prescription databases so that a low, or a high, ratio of inhaled steroids may also indicate shortcomings in diagnostic reliability.

Shortcomings in the quality of the suggested prescribing indicator

Even if we assume some inaccuracy, particularly in the GPs' diagnoses, there still remains a high rate of asthma drugs, including inhaled steroids, that have obviously not been prescribed because of asthma. According to a review of medications before admission to the Toronto University Hospital, 56% of unstable asthma patients, and 44% of stable asthma patients received inhaled steroids — however, 48% of those patients with a diagnosis of unstable COPD also received inhaled steroids.[21] In this case, a ratio of inhaled steroids to bronchodilators would no longer function as an indicator for the quality in treating asthma but as a global measure of how chronic airflow diseases are treated. Although recent hypotheses point to links and overlaps between asthma and chronic obstructive bronchitis,[22,23] such a ratio should not be used as an indicator of quality as long as new treatment strategies are discussed controversially.

There is a debate about differences in the care provided by GPs compared with specialists. For example, in a survey in a large US Health Maintenance Organisation, Vollmer and colleagues[24] found that patients receiving primary asthma care from an allergist were more likely than GP patients to report the use of inhaled steroids. In contrast, patients in a British study were no more likely to receive appropriate asth-

Table 2. The specifity of anti-asthmatic drugs for the diagnosis of bronchial asthma

Drug class[a] [ATC-group or code]		Family Practice				Respiratory practice			
		All causes		Asthma		All causes		Asthma	
		n	%	*n*	%[b]	*n*	%	*n*	%[b]
I	Inhaled beta-2 agonists [R03A]	81	12.2	65	80.3	45	16.2	32	71.1
II	Oral beta-2 agonists [R03CC]	35	5.3	24	68.6	24	8.6	13	54.1
III	Fenoterol + ipratropium (Berodual®) [R03AK03]	95	14.3	68	71.6	43	15.5	10	23.3
IV	Combinations of cromoglycate [R03BC51]	78	11.7	60	76.9	47	16.9	45	95.7
V	Clenbuterol + ambroxol [R03CC63]	57	8.6	26	45.6	1	0.4	1	–
VI	Anticholinergics [R03BB]	14	2.1	9	64.3	2	0.7	0	–
VII	Xanthines [R03DA]	118	17.8	80	67.8	43	15.5	20	46.5
VIII	Cromoglycate/nedocromil [R03BC]	20	3.0	14	70.0	1	0.4	0	–
IX	Inhaled steroids [R03BA]	99	14.9	66	66.7	36	12.9	13	36.1
X	Systemic steroids [H02AB]	67	10.1	43	64.2	36	12.9	12	33.3
	Total	664	100	391	58.9	278	100	136	48.9

[a]Drug classes I to V represent betamimetics in different applications and in single or combined preparations. [b]The specifity of a drug class is calculated as the number of prescriptions for asthma in relation to all causes.

Table 3. Prescription of anti-asthmatic drugs and their marker functions for asthma.

Drug class[a]		General practice			Respiratory practice		
		Asthma (*n*)	Other (*n*)	OR (95% CI)[b]	Asthma (*n*)	Other (*n*)	OR (95% CI)[b]
I	Inhaled beta-2 agonists [R03A]	65	16	2.02[c] (1.14–3.58)	32	13	2.57[c] (1.28–5.14)
II	Oral beta-2 agonists [R03CC]	24	11	1.01 (0.48–2.10)	13	11	1.11 (1.08–2.49)
III	Fenoterol + ipratropium (Berodual®) [R03AK03]	68	27	1.19 (0.74–1.92)	10	33	0.22[c] (0.10–0.47)
IV	Combinations of cromoglycate [R03BC51] (6.86–122.24)	60	18	1.62 (0.93–2.82)	45	2	28.9
V	Clenbuterol + ambroxol [R03BC 63]	26	31	0.35[c] (0.20–0.61)	1	0	–
VI	Anticholinergics [R03BB]	9	5	0.83 (0.27–2.50)	0	2	–
VII	Xanthines [R03DA]	80	38	0.97 (0.63–1.48)	20	23	0.75 (0.39–1.44)
VIII	Cromoglycate nedocromil [R03BC]	14	6	1.06 (0.41–2.85)	0	1	–
IX	Inhaled steroids [R03BA]	66	33	0.91 (0.58–1.43)	13	23	0.46[c] (0.22–0.96)
X	Systemic steroids [H02AB]	43	24	0.81 (0.48–1.37)	12	24	0.40[c] (0.19–0.84)

[a]Drug classes I to V represent betamimetics in different applications and in single or combined preparations. [b]OR>1 indicates a marker function for asthma; OR<1 a marker function against asthma. [c]Significant at the 5% level.

ma medication when seen in an asthma clinic compared with patients managed in general practice only.[17] In two instances, the prescription of fenoterol plus ipratropium, and cromoglycate plus betamimetics in fixed combinations respectively, the respiratory physician's prescriptions in our study were more specific and seemed to be more appropriate than those of his colleagues in general practice. This stronger adherence to guidelines does not necessarily mirror better knowledge, since the respiratory physician's use of inhaled steroids does not seem to comply with current guidelines. Even if it is not possible to generalise the results from the only respiratory physician practice in the region under study, differences between the two types of practices (e.g. in the prescription of cromoglycate plus betamimetics) may be owing to differences in case mix or to the respiratory physician's more precise diagnostic labelling. How such differences affect the marker function of asthma drugs should be studied further.

We conclude that the marker function of drugs is limited in the case of chronic airflow diseases. A ratio of inhaled steroids to inhaled bronchodilators as assumed, for example, by the British Audit Commission,[2,25] seems to be too simplistic a criterion to measure prescribing performance.[13] Even if such a ratio is assessed more accurately in terms of volume rather than prescription items,[4] an improvement in this ratio cannot automatically be considered equivalent to an improvement in asthma care as long as it is unknown whether an increased ratio reflects higher quality in treatment, or a change in diagnostic reliability, and as long as it is unknown which patients are prescribed more corticosteroids and which of them profit from such a change.

In theory, asthma medications serve as markers, or surrogate measures, for diagnoses; the reality seems to be more complex. As long as identification of patients is not, or is only, to a limited degree, made possible through their prescriptions, diagnosis-linked prescribing data should be used whenever possible (e.g. the General Practice Research Database [GPRD]),[26] whereas prescribing data without diagnosis linkage should be interpreted with caution.

References

1. Shelley M, Croft P, Chapman S, Pantin C. Is the quality of asthma prescribing, as measured by the general practice ratio of corticosteroid to bronchodilator, associated with asthma morbidity? *J Clin Epidemiol* 2000; **53:** 1217-1221.
2. Audit Commission. *A prescription for improvement. Towards more rational prescribing in general practice.* London: HMSO, 1994.

3. Lemmer B. Bronchodilator and anti-asthmatic agents. [In German.] In: Schwabe U, Paffrath D (eds). *Drug prescription report 1999*. Berlin, Heidelberg: Springer, 2001: 234-256.
4. Frischer M, Heatlie H, Chapman S, *et al*. Should the corticosteroid to bronchodilator ratio be promoted as a quality prescribing marker? *Public Health* 1999; **113:** 247-250.
5. Schwabe U, Paffrat D (eds). *Drug prescription report.* [In German.] Stuttgart, Jena: Fischer, 1995.
6. Schwabe U. *ATC-Code*. Bonn: Wissenschaftliches Institut der AOK, 1995.
7. SAS Institute Inc. SAS/STAT. *User's Guide* Version 8. Cary, NC: SAS Institute Inc, 1999.
8. Wettengel R, Berdel D, Hofmann D, *et al*. Asthma therapy in children and adults. Recommendations of the German Resepiratory League of the German Society of Pneumology. [In German.]. *Med Klin* 1998; **93:** 639-650.
9. Fabbri L, Caramori G, Beghe B, *et al*. Chronic obstructive pulmonary disease international guidelines. *Curr Opin Pulm Med* 1998; **4:** 76-84.
10. British Thoracic Society, *et al*. The British guidelines on asthma management 1995 review and position statement. *Thorax* 1997; **52:** S1-S21.
11. Point LG, Haaijer-Ruskamp FM. Asthma and asthma medication — a database study of asthma treatment in general practice. *Pharmacoepidemiol Drug Saf* 2000; **9:** S97.
12. Cabana MD, Rand CS, Powe NR, *et al*. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; **282:** 1458-1465.
13. Veninga CC, Denig P, Pont LG, Haaijer-Ruskamp FM. Comparison of indicators assessing the quality of drug prescribing for asthma. *Health Serv Res* 2001; **36:** 143-161.
14. Lagerlov P, Veninga CC, Muskova M, *et al*. Asthma management in five European countries: doctors' knowledge, attitudes and prescribing behaviour. *Eur Respir J* 2000; **15:** 25-29.
15. Legorreta AP, Christian-Herman J, O'Connor RD, *et al*. Compliance with national asthma management guidelines and specialty care: a health maintenance organization experience. *Arch Intern Med* 1998; **158:** 457-464.
16. Veninga CC, Lagerlov P, Wahlstrom R, *et al*. Evaluating an educational intervention to improve the treatment of asthma in four European countries. *Am J Respir Crit Care Med* 1999; **160:** 1254-1262.
17. Roghmann MC, Sexton M. Adherence to asthma guidelines in general practices. *J Asthma* 1999; **36:** 381-387.
18. Keeley D. How to achieve better outcome in treatment of asthma in general practice. *BMJ* 1993; **307:** 1261-1263.
19. Hummers-Pradier E, Hinrichs I, Schoeter M, Kochen MM. Bronchial asthma - expectations and concepts of general practitioners. [In German.] *Z Ärztl Fortbild Qualitätssich* 2000; **94:** 379-387.
20. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Fam Pract* 1999; **16:** 112-116.
21. Jackevicius CA, Chapman KR. Prevalence of inhaled corticosteroid use among patients with chronic obstructive pulmonary disease: a survey. *Ann Pharmacother* 1997; **31:** 160-164.
22. Bousquet J, Chanez P, Vignola AM, Michel FB. Asthma and chronic bronchitis: similarities and differences. [Editorial.] *Respir Med* 1996; **90:** 187-190.
23. Burge PS, Calverley PM, Jones PW, *et al*. Randomised, double-blind, placebo-controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; **320:** 1297-1303.
24. Vollmer WM, O'Hollaren M, Ettinger KM, *et al*. Specialty differences in the management of asthma. A cross-sectional assessment of allergists' patients and generalists' patients in a large HMO. *Arch Intern Med* 1997; **157:** 1201-1208.
25. Bateman DN, Eccles M, Campbell M, *et al*. Setting standards of prescribing performance in primary care: use of a consensus group of general practitioners and application of standards to practices in the north of England. *Br J Gen Pract* 1996; **46:** 20-25.
26. Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998; **45:** 419-25.

Acknowledgment

We are grateful to participating practices for allowing access to their data.