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ORIGINAL ARTICLE

Comorbidity and medication load in adult asthmatics

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Abstract

Objective. To examine comorbidity and the medication load among asthmatics. **Design.** A self-administered postal inquiry. **Setting.** A national register-based random sample of 6000 subjects aged 16 years or older entitled to special reimbursement for anti-asthmatic medication in Finland. **Subjects.** A total of 4690 subjects with clinically diagnosed asthma. **Main outcome measures.** Reporting of doctor-diagnosed chronic diseases and the number of prescription medicines used by asthmatics. **Results.** Two-thirds of the subjects ($n=2952$, 63%) reported other diseases in addition to other chronic pulmonary diseases and allergies. Musculoskeletal and cardiovascular disorders were the most common, increasing with age. Allergies were most frequent among the young asthmatics. Nearly all the subjects ($n=4444$, 95%) took at least one anti-asthmatic medicine, and two out of every three ($n=3051$, 65%) received other prescription medicines, most commonly cardiovascular drugs or analgesics. Some 41% ($n=1938$) of all the asthmatics and as many as 21% of the young adults ($n=269$) were taking at least five prescription medicines concomitantly. The total medication load increased with age. **Conclusion.** The load of comorbidity and prescribed medication is heavy in adult asthmatics of all ages. Thus asthmatic patients should best be treated by GPs, while pulmonary specialists work as consultants and take care of the most severe cases.

Key Words: Asthma, comorbidity, medication, polypharmacy

General practitioners (GPs) treat patients with complex health problems without focusing exclusively on individual clinical disorders. Asthma is one of the most frequent chronic disorders seen in a primary care physician's consultation room. This is in particular true in Finland, where the national Asthma Programme, launched in 1994, emphasizes the central role of primary health care in its treatment [1,2]. GPs were responsible for treating 75% of adult asthmatics in 2000, with specialized care being reserved mainly for the most severe cases [2].

Along with ageing of the population, comorbidity [3] and the number of medicines taken [4,5] tend to increase. This leads to problems of adherence to treatment, for instance [6,7], and a risk of adverse

reactions and harmful interactions if the medication is increased further [5,8–10]. A physician should

Asthma is one of the most frequently seen chronic diseases in GPs' consultation rooms.

- The load of comorbidity and prescription medication is heavy enough to require careful consideration when treating an asthmatic patient.
- Comorbid conditions and their medical therapies may cause problems with adherence to treatment and interfere with the control of asthma.
- GPs are in key position to manage asthmatic patients with several concurrent diseases.

consider these aspects when treating subjects suffering from several concurrent diseases.

The objective of the present study was to examine comorbidity and total load of prescription medication among adult asthmatics in Finland and to discuss the implications of the findings for clinical practice and for the organization of asthma treatment.

Material and methods

Setting

The Finnish Social Insurance Institution (SII) maintains a nationwide register of patients with certain defined chronic diseases who, instead of the ordinary reimbursement (50%), are entitled to a special 75% refund on related medicine expenses. Inclusion presupposes that the patients' condition meets certain diagnostic and severity criteria, for which a medical certificate is required. In the case of asthma, the certificate must be signed preferably by a specialist in pulmonary medicine, internal medicine, paediatrics, or allergology. As presented in our previous report [2], the criteria for a special refund for anti-asthmatic medicines are:

- a need for regular anti-asthmatic medication for over 6 months, combined with
 - a minimum increase of 15% in peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV1) in a bronchodilation test (minimum 50 l/min or 0.15 l in adults); or
 - a decrease in PEF or FEV1 by a minimum of 15% during a physical strain test (minimum 50 l/min or 0.15 l in adults); or
 - fluctuation of over 20% from the peak value in 24-hour PEF monitoring (minimum 50 l/min in adults).

Data

In the year 2000 a total of 124 817 subjects aged 16 years or over were entitled to the special 75%

refunds on medicines for chronic asthma and similar chronic obstructive pulmonary diseases (prevalence 3.0%). A representative systematic sample of 6000 subjects was drawn from this population. A questionnaire was mailed to the subjects in May 2000, containing items on medication, doctor-diagnosed morbidity, and the use of health services. The method has been described in detail earlier [2].

A total of 4956 subjects (83%) replied to the inquiry. The subjects were asked to report their clinical pulmonary diagnoses from among the following: bronchial asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema. The final series comprised 4690 persons with asthma, 1785 (38%) men and 2905 women (Table I). Their mean age was 54.4 years (SD 17.6 years), the figures being approximately the same for both sexes.

Information on the occurrence of other diseases was collected by means of the question: "Do you have any of the following chronic diseases diagnosed by a doctor?", followed by a list of 10 conditions, as presented in Table II.

The use of anti-asthmatic medicines at the time was assessed by presenting a list of all 35 brand names available on the Finnish market [11]. The medicines represent 20 substances classified in the Anatomical Therapeutic Chemical classification index (ATC) under the code R03 (Drugs for obstructive airway diseases) [11]. The substances were classified into nine categories, as presented in Table III. In addition, the subjects were asked to name all the other prescription medicines that they were taking.

Statistical analyses

The statistical computations were performed using the SPSS 11.5 software package. Since the distributions of the occurrences of the most commonly reported chronic diseases other than obstructive pulmonary ones were about the same among the asthmatic men and women, the results were com-

Table I. The series of patients with doctor-diagnosed asthma, by age and gender.

	Age						Total	
	16–44 years		45–64 years		≥ 65 years		n	%
	n	%	n	%	n	%		
Men	482	37	671	37	632	41	1785	38
Women	826	63	1160	63	919	59	2905	62
Total	1308	100	1831	100	1551	100	4690	100
Distribution by age in total (%)		28		39		33		100

Table II. Reporting of doctor-diagnosed chronic diseases (*n*) in the inquiry among Finnish adult asthmatics.

	Age						Total	
	16–44 years		45–64 years		≥ 65 years		<i>n</i>	%
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
Chronic obstructive pulmonary diseases ¹	1308	100	1831	100	1551	100	4690	100
Asthma with no other obstructive pulmonary disease	1234	94	1525	84	1062	69	3821	81
Asthma with at least one other obstructive pulmonary disease	55	4	261	14	422	27	738	16
Chronic bronchitis	53	4	188	10	311	21	552	12
Emphysema	5	<1	70	4	146	9	221	5
COPD	1	<1	77	4	153	10	231	5
Doctor-diagnosed allergy	1050	80	1068	58	714	46	2832	60
At least one of the other defined diseases ^{1,2}	448	34	1252	68	1252	81	2952	63
Back problems	218	17	669	37	694	45	1581	34
Osteoarthritis	38	3	399	22	517	33	954	20
Rheumatoid arthritis	10	<1	73	4	135	9	218	5
Osteoporosis	8	<1	84	5	201	13	293	6
Hypertension	65	5	563	31	630	41	1258	27
Coronary artery or other heart disease	19	1	252	14	677	44	948	20
Diabetes	18	1	154	8	204	13	376	8
Mental disorders	42	3	124	7	60	4	226	5
Eye diseases	49	4	166	9	461	30	676	14
Migraine	186	14	237	13	103	7	526	11

¹The sum of reported other diseases may exceed the total number of subjects, because some subjects reported more than one disease on the list.

²At least one of the following diseases: Back problems, Osteoarthritis, Rheumatoid arthritis, Osteoporosis, Hypertension, Coronary artery or other heart disease, Diabetes, Mental disorders, Eye diseases, or Migraine.

bined in this respect. Statistical significances were calculated with the Pearson chi-squared test and a level of $p < 0.05$ was used. The 95% confidence interval (CI) was calculated for the difference in the mean number of medicines.

Analysis of non-response

Altogether 85% of the women and 79% of the men responded to the inquiry. Subjects aged 45 years or over were slightly over-represented in the final material. There was no regional response bias towards any part of the country. The occurrence of a special refund for medication for major chronic diseases in the SII register was the same among the respondents and non-respondents, except for psychoses and rheumatoid arthritis, which were somewhat under-represented in the final series.

Ethical requirements

The study was conducted in compliance with the requirements of the Ethical Committee of the Faculty of Medicine, University of Oulu, Finland.

Results

There were 738 subjects (16%) for whom asthma was accompanied by at least one other chronic

obstructive respiratory disease, this being more common among the men ($n = 353$, 20%) than the women ($n = 385$, 14%) ($p < 0.0001$), and the proportion increased with age (see Table II).

Three out of every five subjects ($n = 2832$, 60%), and as many as 80% ($n = 1050$) of the young adults (aged 16–44 years) reported a doctor-diagnosed allergy (see Table II). Other chronic diseases apart from obstructive pulmonary diseases or allergies were reported by 63% of the asthmatics ($n = 2952$). Of the defined diseases, musculoskeletal ($n = 2100$, 45%) and cardiovascular ones ($n = 1722$, 37%) were the most common in all age groups. Elderly asthmatics (aged 65 years or over) reported these diseases most frequently, but also every second middle-aged adult ($n = 887$, 48%) and one out of five among the young adults ($n = 246$, 19%) reported musculoskeletal problems, while cardiovascular diseases were fairly rare in this age group.

Nearly all the subjects ($n = 4535$, 97%) were taking at least one prescription medicine, including anti-asthmatics. The mean number of prescription drugs was 4.5 per patient, and the figure again increased with age, from 3.2 among the young adults to 5.6 among the elderly. One out of every five subjects ($n = 1044$, 22%) was taking at least seven prescription medicines, as did every third elderly subject.

Table III. Number of prescription medicines in use among Finnish adult asthmatics (*n*), by age.

Total number of medicines	Age						Total (<i>n</i> = 4690)	
	16–44 years		45–64 years		≥ 65 years		<i>n</i>	%
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
0	72	5	62	3	21	1	155	3
1–4	967	74	992	54	638	41	2597	56
5–6	183	14	391	22	320	21	894	19
≥ 7	86	7	385	21	573	37	1044	22
Mean (SD)	3.2 (1.9)		4.6 (2.8)		5.6 (3.1)		4.5 (2.9)	
95% CI of the difference of means ²			1.23–1.58		0.85–1.24			
			2.26–2.64					
Number of anti-asthmatics in different categories ¹	Age						Total (<i>n</i> = 4690)	
	16–44 years		45–64 years		≥ 65 years		<i>n</i>	%
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
0	88	7	96	5	62	4	246	5
1	139	11	157	9	173	11	469	10
2	747	57	803	44	614	40	2164	47
3	243	18	460	25	421	27	1124	24
4	68	5	196	11	175	11	439	9
≥ 5	23	2	118	6	107	7	248	5
Mean (SD)	2.1 (1.0)		2.5 (1.3)		2.6 (1.3)		2.4 (1.2)	
95% CI of the difference of means ²			0.31–0.48		–0.44–0.13			
			0.41–0.59					
Number of other medicines	Age						Total (<i>n</i> = 4690)	
	16–44 years		45–64 years		≥ 65 years		<i>n</i>	%
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
0	669	51	597	33	373	24	1639	35
1–2	444	34	632	34	395	26	1471	32
3–4	145	11	325	18	298	19	768	16
≥ 5	50	4	276	15	486	31	812	17
Mean (SD)	1.1 (1.5)		2.1 (2.2)		3.1 (2.7)		2.1 (2.4)	
95% CI of the difference of means ²			0.87–1.15		0.84–1.17			
			1.85–2.17					

¹Inhaled short-acting β_2 -agonists (fenoterol, salbutamol, and terbutalin), inhaled long-acting β_2 -agonists (formoterol and salmeterol), inhaled anticholinergics (ipratropium bromide and oxitropium bromide), inhaled corticosteroids (beclomethasone dipropionate, budesonide, and fluticasone dipropionate), inhaled cromones (sodium cromoglicate and nedocromil), systemic corticosteroids (methyl prednisolone, prednisone, and prednisolone), theophylline and aminophylline, leucotriene modifiers (montelukast and zafirlukast) and ephedrine.

²95% Confidence interval of the difference of mean numbers of medicines between age groups, calculated with the independent-samples t-test.

Anti-asthmatic medication was used by 4444 subjects (95%), and the number of these drugs also increased with age (see Table III). There were 248 (5%) persons who were taking at least five types of anti-asthmatic medicine concomitantly.

Two out of every three subjects (*n* = 3051, 65%) were receiving prescription medicines other than anti-asthmatic ones, the proportion being 49% among the young adults (*n* = 639), 67% among the

middle-aged (*n* = 1234), and 76% among the elderly (*n* = 1178).

Cardiovascular medicines and analgesics were the most common of these other medicines, and became more common than ever with advancing age (Table IV). On the other hand, anti-allergic medicines were taken most frequently by the young adults and their use decreased with advancing age.

Table IV. Use of prescription medicines other than anti-asthmatics among Finnish adult asthmatics (*n*), by age and gender.

Medicine	Age						Total (<i>n</i> = 4690)		Men (<i>n</i> = 1786)	Women (<i>n</i> = 2905)	p-value ¹
	16–44 years		45–64 years		≥ 65 years		<i>n</i>	%	%	%	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%					
Anti-allergics	273	21	218	12	114	7	605	13	8	16	<0.0001
Antihistamines for systemic use	189	14	123	7	80	5	392	8	5	10	<0.0001
Nasal preparations ²	102	8	117	6	42	3	261	6	4	7	<0.0001
Dermatological corticosteroid preparations	3	<1	8	<1	5	<1	16	<1	<1	<1	0.281
Cardiovascular therapy ³	23	2	312	17	534	34	869	19	17	20	0.010
β-blocking agents	8	<1	70	4	97	6	175	4	3	4	0.104
Agents acting on the renin-angiotensin system	10	<1	113	6	90	6	213	5	5	4	0.573
Analgesics ⁴	75	6	293	16	387	25	755	16	13	18	<0.0001
Anti-inflammatory analgesics ⁵	46	4	186	10	283	18	515	11	10	12	0.054
Paracetamol	20	2	65	4	67	4	152	3	2	4	<0.0001
Opioids	13	1	66	4	68	4	147	3	3	4	0.039
Systemic corticosteroids in regular use ⁶	108	8	290	16	227	15	625	13	11	15	<0.0001
Antidiabetics	9	<1	61	3	62	4	132	3	3	3	0.751
Agents acting on thyroid function	17	1	122	7	91	6	230	5	1	7	<0.0001
Psychotropics ⁷	40	3	140	8	139	9	319	7	5	8	<0.0001

¹p-values for the prevalence among men and women are calculated with the Pearson chi-squared test.

²Non-steroidal nasal sympathomimetics, nasal corticosteroids, and their combinations with sympathomimetics in systemic and nasal therapy.

³Cardiac glycosides, nitrates, diuretics, β-blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system, other antihypertensives, and serum lipid reducing agents.

⁴Anti-inflammatory analgesics, acetylsalicylic acid (ASA) and its combinations, low-dose ASA, other analgesics and antipyretics, and opioids.

⁵Anti-inflammatory analgesics, ASA and its combinations, and low-dose ASA.

⁶Prednisone, prednisolone, and methylprednisolone.

⁷Antipsychotics, anxiolytics, hypnotics, and antidepressants.

There were users of systemic corticosteroids in all the age groups of asthmatics, but their use was most common among the middle-aged (45–64 years) ($n = 290$, 16%) and elderly subjects ($n = 227$, 15%).

Discussion

Principal findings

The load of comorbidity and prescription medication in adult asthmatics is heavy enough to require careful consideration when treating an asthmatic patient. Our observations gain support from previous studies in primary care [4,5,12], although we did not compare comorbidity or medication load with other population groups.

Strengths and weaknesses

One strength of our work lies in the use of a register-based random sample from the entire adult population with clinically diagnosed, persistent asthma fulfilling certain severity criteria and treated with long-term anti-asthmatic medication. It follows that subjects with mild asthma and with occasional or seasonal anti-asthmatic medication are not included.

The response rate in the questionnaire study was high, with no major response bias. The questionnaire method has earlier been found to be fairly reliable for obtaining health status information [13].

Since there was a high frequency of doctor-diagnosed allergy, especially among the young adults, it is possible that some asthmatics, even ones with intrinsic asthma, may have assumed their disease to be of allergic origin. On the other hand, some recent studies have reported similarly high prevalence figures for allergy in adult asthmatics [14,15].

Another problem may be the differentiation of asthma from other chronic obstructive pulmonary diseases. Chronic bronchitis or emphysema may have been misclassified as asthma due to diagnostic problems, or else asthma may have developed into an irreversible obstruction later, after the diagnosis. A third possibility is that subjects may have misunderstood the diagnosis and reported it incorrectly.

Comorbidity and medication load

Our results indicate that comorbidities are common in adult asthmatics of all ages and, surprisingly, even in young adults. Their diseases require mainly occasional or seasonal attention, however, as in cases of migraine or allergy, while those among the elderly need more longstanding treatment. Other diseases

will require attention and clinical skills on the part of the physician, and these may reduce the role of asthma in the treatment regime. From the viewpoint of both the asthmatic patient and the general practitioner, the occurrence of diabetes or coronary heart disease, for instance, can be the most important target of treatment, leaving asthma in a secondary position.

The physician should aim at keeping the medication as simple as is therapeutically possible. Asthma is mostly treated with more than one medicine [2], and other diseases further increase the number of medicines. This occurs especially often among the elderly, who have the heaviest medication load [4,5]. The use of other prescription medicines was also common among the middle-aged, though anti-asthmatics still comprised half of their total medication.

The risk of adverse reactions and harmful interactions increases with the number of drugs in use [5,8–10], and elderly patients are most sensitive to such problems [16]. Fortunately, inhalation anti-asthmatics are unlikely to have clinically relevant interactions with other medicines [17,18]. On the other hand, other medical therapy may interfere with the control of asthma. Such groups of medicines include agents acting on the renin–angiotensin system [19], β -blocking agents and NSAIDs [7]. The prescription of these medicines was relatively rare in our material.

Systemic corticosteroids are often indispensable for managing severe forms and exacerbations of asthma, but they may be needed for a variety of other diseases as well. A change in the steroid dosage for any indication may affect the therapeutic equilibrium of asthma.

As new drugs become available and treatments more complex, therapeutic regimens are increasingly likely to involve technical and compliance problems [6]. The use of several anti-asthmatic drugs with their different devices may threaten the patient's ability to manage inhalation therapy. Besides such technical problems, the concurrent use of several medicines does increase medication costs to the patient, which may lead to suboptimal implementation of the necessary treatment.

Since we studied only the use of prescription medicines, OTC drugs such as mild NSAIDs, and similarly herbal remedies, remained outside our material. Self-treatment with non-prescription products is common among adults with asthma and has been associated with an increased risk of hospitalization [20]. These products will further increase the number of medicines and may interfere with the control of asthma.

Organizational aspects

The Finnish Asthma Programme launched in 1994 shifted the main responsibility for asthma care from specialists to the primary health care sector [1]. This reorganization has been reasonable with regard to high comorbidity, because GPs are used to treating patients who have several concurrent diseases. The risk of potential drug interactions is also lower when the patient is treated by a single physician [21]. GPs, having established and trustful relationships with their patients, can potentially take account of psychosocial factors that may have an influence on the symptoms [22]. Specialists have an important role in supporting the primary care sector in the form of consultations and the planning of guidelines for treatment and in taking care of the most severe cases.

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