



PHARMO REPORT

INNOVATIONS IN PHARMACOTHERAPY



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Herings, R.M.C., Panneman M.J.M., Graag de E.J.

Innovations in Pharmacotherapy

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INNOVATIONS IN PHARMACOTHERAPY



PHARMO Institute

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Dr. R.M.C. Herings : PHARMO Institute, Utrecht, The Netherlands
Department of Pharmaco-epidemiology & -therapy of
Utrecht University, The Netherlands

Drs. M.J.M. Panneman: PHARMO Institute, Utrecht, The Netherlands

Drs. A.C. Lodder : PHARMO Institute, Utrecht, The Netherlands

E.J. de Graag : PHARMO Institute, Utrecht, The Netherlands

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1 SUMMARY AND CONCLUSIONS

Pharmacotherapy is one of the most applied forms of medical treatment. The implementation of pharmacotherapy in clinical practice is constantly developing. There are concerns about the greatly increased use of drugs and the inherent financial consequences in clinical practice.

This study's objective is to conduct a macro-survey into the developments in pharmacotherapy during the past decade focussing on volume and cost development as well as the trends in the nature and extent of hospitalisations, hospital procedures and consultations of medical specialists. To meet this objective three case studies were selected namely; acid related diseases, diabetes mellitus, asthma and COPD. The trends in volume and cost of pharmacotherapy in these diseases were researched and the findings have been related to major changes in therapeutic insights. Parallel to this the hospitalisations related to these three diseases have been discussed. Although the nature and aetiology of the studied different are quite different some developments showed important similarities.

Volume growth related to number of treated patients

The results of the studies show that the increase in volume and cost of medication for all three diseases mainly the result of an increase in the number of treated patients. The demographic changes were hardly explanatory. Concerning asthma, COPD and diabetes there is strong evidence that the increase is consistent with the efforts made to facilitate early detection and diagnostics. The increase in the use of proton-pump inhibitors raises questions concerning the assessment of its use. Here, the results of this study show that approximately 25% of the use of these medications can be attributed to patients using proton-pump inhibitors for prevention and treatment of acid-related gastrointestinal complaints related to the use of NSAID.

Clinical practice follows therapeutic insights

The developments in pharmacotherapy slowly but clearly follow new pharmacotherapeutic insights. In general the results of our study clearly indicate that a more applicable pharmacotherapy is used on diabetics, that patients with asthma and COPD receive medication at a much earlier stage, to combat the underlying inflammations inherent to lung diseases and that proton-pump inhibitors are the most effective means to reduce peptic acid secretion. Despite this the average cost of pharmacotherapy per patient in time only shows a slight increase (see next table).

Patients and pharmaceutical treatment costs for acid-related disorders, diabetes and asthma/COPD in the period 1991-1998 in The Netherlands.

	1991	1992	1993	1994	1995	1996	1997	1998	V*
Costs Gastroprotective drugs**	389	473	534	588	633	628	648	700	9%
Observed Users (x 1,000)	1,089	1,160	1,234	1,306	1,317	1,376	1,459	1,549	5%
Average cost per user***	357	408	433	450	481	456	444	452	4%
Costs Antidiabetic drugs**	159	183	207	225	221	209	227	275	8%
Observed Users (x 1,000)	248	262	276	295	307	323	344	371	6%
Average cost per user***	641	698	750	763	720	647	660	741	2%
Costs Asthma & COPD drugs**	313	351	408	449	482	518	532	556	9%
Observed Users (x 1,000)	727	771	843	910	948	998	1,106	1,200	7%
Average cost per user***	431	455	484	493	508	519	481	463	1%

* V: average yearly increase in the period 1991-1998 [:($\$$ yearly percentage of increase)/n]
** in million guilders
*** in guilders

Number of hospital admissions decrease relatively

Hospital admissions are decreasing relative to the decrease in the number of patients. Much has happened in Dutch hospitals during this study's observation period. However, the trends observed validate in-depth research into the precise relationship between hospitals and pharmacotherapy. In all cases the observation can be made that treatment has strongly intensified on an outpatient basis.

Recapping, the conclusion can be made that the years 1991-1998 have been the scene of treatment intensifying. There seems to be an added awareness to treat the patient early and intensively. When placing the increase of volume and cost in context, these influences must be taken into account.

2 INTRODUCTION

Scientific research changes therapeutic insights. Old drugs are either substituted by new ones, or improved administrations or treatment regimens of well-known drugs are introduced. Drugs are taken from the market because of the occurrence of side-effects that negatively unsettle the balance between effectiveness and safety, or they disappear from the pharmacotherapeutic assortment when they are found to be ineffective after all.

At the same time, the stakeholders of pharmacotherapy (among which, governments, industries, insurance companies and professionals), each from their own point of view and interest, try to get a grip on the medication dossier. In short, insight in optimal pharmacotherapy is changing constantly.

A closer look at pharmacotherapy itself reveals that the medication dossier has changed drastically during the past decade. The concept of evidence-based medicine catches on. Treatment protocols, formularies (FTO), and treatment standards, were introduced as a guideline for the daily routine in general practice; and in many therapeutic fields the results became available of extensive (lengthy) clinical studies in which different therapeutic strategies were compared to each other. New scientific fields developed (pharmaco-epidemiology, -economy) aiming to obtain a better insight into the clinical and economic value of drugs when used in daily practice, after approval of licensing authorities.

The cost of drugs increased 34% from 4.9 billion to 6.4 billion guilders (2.2 billion to 2.9 billion Euros) in the period 1991-1998, an average cost increase of 4-5% annually (JOZ). This cost increase causes political concern, which has led to a several advices and projects to stimulate a new (government) policy. Several recent studies showed clearly how unruly the medication dossier is, not in the least due to the complex coherence between the different parts of the drug system is not always clearly acknowledged. Minor interventions can have major results, while apparently strong interventions seem to have hardly any influence whatsoever. An example hereof is that the removal of drugs from the insurance package can lead to substitution with other drugs.

Presentation of the question and perspective of the study

This study's objective is to conduct a macro-survey into the developments in pharmacotherapy during the past decade, paying special attention to changes in volume- and costs, as well as trends in the nature and number of hospital admissions, related therapy, and consultations.

To comply with this objective, three diseases are selected as 'representative' cases, namely acid-related diseases, diabetes mellitus, and asthma and COPD. The trends in volume and costs of pharmacotherapy have been studied thereof, and the findings have been related to major changes of the therapeutic insights into these diseases introduced in last 5-10 years. Parallel to it, costs and number of hospital admissions related to these three diseases have been explored.

We would like to emphasise that we are dealing with macro surveys particularly meant to get a better interpretation of the developments in the pharmacotherapy. Here and there, possible explanations are put forward, but the followed methodology has been primarily aimed at clarifying the interrelationship between the various developments in the medical treatment of a number of important chronic diseases. Insight into this interrelationship is important for a sound judgement regarding the previously mentioned problems of- and possible solutions for- the medicationdossier.

The survey is based on data in the PHARMO-system. In the next chapter, the followed methodology and methods of calculation are more closely examined. Then, in the chapters 4, 5, and 6, the results will be discussed of: acid-related diseases, diabetes mellitus, and asthma and COPD.

3 METHODS, DEFINITIONS AND DATA SOURCES

3.1 Introduction

In this chapter, a general description is given of the methods, definitions, data sources, choices and assumptions that have been used for this particular survey. The survey aims to outline the developments of the pharmacotherapy- in terms of both volume as costs- for acid-related diseases, diabetes mellitus, and asthma and COPD. Also, the use and the involved costs of hospital facilities (beddays, procedures, operations and consultations) related to each of these diseases have been outlined. The next chapters shall explain how the use and costs of pharmacotherapy, as well as the hospital facilities have been calculated.

The general point of departure for the calculation are the costs from the third party payer perspective. These are the actual reimbursed costs (including tax) by health insurers on basis of CTG¹ rates (pharmaceutical help, hospital treatments). In practice, the rates are not necessarily the actual costs, but are meant as financing systematics. Moreover, in calculating the costs of hospital admissions, it has to be taken into account that various extra charges may be incorporated such as, for example, investment expenditures for new buildings by which the daily hospital charges for in-patients can differ.

3.2 Choice of diseases

To answer the question put forth in this study, three diseases have been selected. The selection was based on a four criteria:

1. It should be feasible to be able to identify patients with a specific disease on the basis of the use of certain specific drugs.
2. The incidence/prevalence of the disease needs to be sufficiently high to play a significant role in the consumption of care and related costs.
3. In relation to the disease, new drugs or newpharmaco-therapeutic treatments should have been introduced in the past 5-10 years.
4. The disease needs to be strongly associated with demographic factors and changes thereof in the near future.

¹ CTG: Institute in charge of defining tariffs for health resources in the Netherlands

On basis of these criteria, the acid-related diseases were selected because of the increasing use of proton-pump inhibitors. The choice for diabetes was made because of the influence of the ageing population and the changed insights in treatment (early diagnosis, tighter glucose regulation). Asthma and COPD are selected because of the expected increase through ageing, the changed insights regarding the role of inflammation during the treatment, and the introduction of long-term β -agonists.

3.3 Data sources

For this survey, use was made of the PHARMO-system. The PHARMO-system is a system developed by Utrecht University for the benefit of pharmaco-epidemiologic research by which both medication-as well as hospital data are filed since 1986 [1]. The system is based on data derived from the public pharmacy, which are controlled by the pharmacy data bank U-Expo, and data from the LMR, controlled by Prismant (formerly SIG Care information). Both databanks, as well as the PHARMO database, are located in Utrecht.

The pharmacy databank U-Expo in the PHARMO-system consists of a representative sample survey of 30 pharmacies in eight regions scattered over the Netherlands of which the population denominator has been accurately described [1]. It covers all 320,000 inhabitants regardless of insurance form, which corresponds to about 2% of the Dutch population. All medication data in the U-Expo are encoded according to standards based on the drug reference databank of the Dutch Association for the Advancement of Pharmacy (KNMP). This makes it possible to identify and classify drugs in time, both on basis of national and international encodings, as by individual active components and route of administration. In principal, the U-Expo collates primarily medication given on prescription. Of each dispensed drug, the dispensing date, the prescriber, the daily dosage, dispensed quantity and legend duration of use are known. At the end of 1998, the U-Expo included more than 50 million prescriptions, prescribed by general practitioners, dozens of medical specialists, dentists, and others with a prescription license.

The Dutch National Medical Registration (LMR) is a frequently used source of data about hospital admissions in the Netherlands. The LMR is managed by the Prismant organization foundation in Utrecht. Since 1991-1992, the LMR's periods of responsibility (POR) are determined by the specialist in attendance. Each POR consists of a primary diagnosis and possible treatments. Afterwards, that is after discharge from the hospital, the reason for hospital admission and the POR is determined and recorded as primary diagnosis. All diagnoses are encoded according to the International Classification of Diseases (ICD-9-CM). The treatment considered to be the most important in retrospect, will be classified as the primary treatment. This is usually the treatment

pertaining to the primary diagnosis. For this study, admissions have been selected on the basis of the primary diagnosis. This means that only those treatments are included in the survey that are mentioned in records with a primary diagnosis for the relevant disease.

The assumption is made that for the specific selected diseases, the data regarding the drug use and health resource utilization originate from the same source population. Also, because all records in PHARMO are ultimately classified on patient level, estimates of the drug use (and the relevant costs) can be made per patient. The mentioned data files are made anonymous and submitted to strict rules of control and independent supervision.

3.4 Use of drugs

The volume of drug use is usually expressed in various measures. Probably the most well known and most obvious measure is the so-called prescription to which a compensation fee is linked. In this report, the use of drugs is represented in the estimated number of dispensed prescriptions in the Netherlands. Only drugs that have been dispensed by the public pharmacy are considered. This measure is the same as the one being used by the SFK and the GIP, to other organization that collates drug dispensing data in the Netherlands. Next to the number of prescriptions, the use is also expressed in the number of patients that at any time did use a prescription X in a certain year. This measure can be indicated as the year prevalence. In addition to this, use is made of the point prevalence, reflected as the number of patients exposed to drugs on a particular moment in time, here defined as the first Wednesday in the month October of a certain year as reference date. All figures of drug use have been expressed as the total number of prescriptions or persons in the Netherlands after standardization on age and gender in the year concerned.

The drug costs are calculated on basis of reimbursed prescriptions in the concerned years from the participating pharmacies as filed in the PHARMO-system. This amount consists of a fee, stimulus, margin, prescription compensation and includes VAT.

3.5 Hospital data

For this study a model has been developed to calculate the costs of a single hospital admission on the basis of data (admissions according to diagnosis, patient-days, treatments) as registered at the LMR. By calculating the costs, three cost components were taken into account: hospital days, operations and procedures, and consultations by medical specialists. These care units have been multiplied with the fees differentiated according to specialism and year and subsequently added.

Days of hospital accommodation

In the daily in-patient accommodation charges, which we used, all hospital costs (including intramural drug use and location-bound costs) are included, except the costs of treatments for the hospital and the fees for the specialists. Each hospital has its own specific agreement with the COTC regarding the in-patient price-fixing. To determine the average in-patient price, six general and eight academic hospitals were asked for their in-patient rates.

For 1998, the average in-patient charge was then calculated to have been Nfl. 1,000 daily for general hospitals and Nfl. 1,500 for academic hospitals with, in both cases, a daily surcharge of Nfl. 1,500 for admission at the Intensive Care ward. In turn, these amounts obtained with an index from the COTC were extrapolated to the years 1991 up and including 1998. For the compensation of in-patient charges, no differentiation is made between patients covered by National Health Insurance, or privately-insured patients.

In academic hospitals, the specialists in employment receive a daily in-patient contribution for a National Health Service patient. This contribution can be seen as a correction for lacked income of the specialist in employment.

Treatments

The type of treatment at hospitals is registered in the Dutch National Medical Registration (LMR) in a medical encoding, the CVV, which has been introduced to all hospitals in the Netherlands in 1991. When declaring treatments in hospitals, however, this code is not used, but CTG-rates are being used instead. For the calculation of the treatment costs in this study, we, therefore, made use of the study 'Costs of diseases in the Netherlands 1994', in which the costs have been calculated according to the CVV-code [2]. The costs for the treatments have been calculated on the basis of a flat rate and a fee that covered about 25% of the total costs per treatment. The latter has been indexed and calculated on an annual basis. The fixed part has been considered to be constant over the years.

Consultations

In principle, a distinction is made between first-, consecutive-, and intercolleagial consultations. For the first two, up till 1997, a card system was used for National Health Care patients and a consultation fee for private patients. In connection with a harmonisation as per 1-1-97, a card system was introduced for both types of insured parties. This is the reason that since 1997, equal rates exist for National Health Care- and privately- insured patients. The intercolleagial consultations are covered at this moment by clinical fees that deviate with respect to compensation of first- or consecutive consultations. The costs of these intercolleagial consultations are estimated and indexed on basis of COTC fees for the calculations of the period 1991-1998.

3.6 Population Attributive Risk

The population attributable risk (PAR) is used to estimate the proportion of a disease that can be attributed to the exposure of an etiological factor (e.g., drug use, smoking, alcohol use etc) [3]. The PAR is therefore an estimate of the fraction of disease that could have been prevented in the complete absence of the determinant. For the calculation of a PAR, use is made of the formula $PAR = 100\% * (p(OR-1) / (p(OR-1) + 1))$ (condition: $OR > 1$, $OR = \text{Odds Ratio}$), by which p means the prevalence of the use of the relevant drug in the PHARMO-population, and the OR is an estimate of the relative risk. The relative risk and the outcome are usually age-dependent. Correction therein can be made with a Mantel-Haenszel procedure (3). The PAR is calculated per sex stratum and age stratum of five years. For extrapolation to the Dutch population, the age- and sex-specific PAR's have been used for standardization. The so-calculated standardized PAR may therefore deviate from the PAR in the PHARMO population. Estimates of the absolute number of disease cases that may be attributed to the use of drugs are based on age- and sex-specific PAR's.

3.7 Literature

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2. Polder, J., et al. *Kosten van Ziekten in Nederland 1994.1997*, Rotterdam: Instituut voor Maatschappelijke Gezondheidszorg, 296.
3. Coughlin, S.S., et al. *Attributable risk estimation in case control studies*, *Epidemiologic Reviews*, 1994, 16(1), 51-64.

4 ACID-RELATED DISEASES

4.1 Background

Acid-related diseases are a number of disorders for which either regulation of the acidity is indicated, protection against the erosive effect of acid, or were acid secretion inhibitors (including all antacids) relieve the complaints. These disorders differ in nature and seriousness among which, for instance, light dyspeptic complaints, gastritis, reflux oesophagitis, up to and including peptic ulcers. The total prevalence of acid-related disorders is difficult to estimate. The prevalence of dyspeptic complaints is widely spread and varies from 19-41% [1]. Only part of these patients visits the general practitioner; and notwithstanding an additional examination, the cause is not always found (functional dyspepsia). On the other hand, the yearly incidence of peptic ulcers is estimated to be 2 per 1.000 annually. About one out of ten persons uses a gastric-acid-secretion inhibitor at least once a year. This adds up to 1.5 million person in the Netherlands annually.

Drugs that are used for acid-related disorders have in common that they are acid-inhibiting and/or protective against the impact of acid, and in this chapter shall hereupon be referred to as gastroprotectives (GPA). In the eighties and nineties various new drugs were introduced with quite different mechanisms of action. The most important group are the proton-pump inhibitors. These drugs inhibit the acid-production in a forceful and prolonged manner. The mechanism of the proton-pump inhibitors is based on the inhibition of the enzyme H^+/K^+ -ATP-ase, causing the decrease of both the basal- and food-induced acid secretion. At this moment, the proton pump inhibitors are the most effective acid-inhibitors and a major innovation in the treatment of acid-related disorders. Next to the proton-pump inhibitors, the prostaglandine-analogues (like misoprostol) have also been introduced in the past ten years.

4.2 Selection criteria of patients

To study the pharmacotherapeutic development of acid-related diseases, patients were selected on basis of the use of GPA [2]. These include drugs that are classified in ATC-group A02, including the pro-kinetic drugs cisapride and domperidon. In general, these drugs are labelled for the treatment of reflux oesophagitis, gastritis, ulcus duodenum, ulcus ventriculus or related disorders. Patients were selected for this study conditional that they used a drug from this group at least once in the year of study. Furthermore, all hospital admissions in The Netherlands were selected with a main diagnosis: ICD-codes 530-537. Of these patients, the volume and costs of the use of GPA were extracted from the Database for the period 1991-1998. Also the number of hospital admissions and inherent costs were studied.

4.3 Drugs

Volume development 1991-1998

Table 4.1 shows the development of the total number of GPA prescriptions in The Netherlands for the period 1991-1998. Since 1991 its use increased with an average of 7% annually. Noteworthy is the increased use of proton-pump inhibitors, the use of which has continued to grow strongly since 1991. At the end of the observation period, we also see the increase of helicobacter Pylori (HP) eradication treatments. The use of H₂ antagonists has been decreasing since 1994. Also the use of mucosa protectives is decreasing, while the use of antacids hardly has changed. The growth in the category of other drugs is mainly caused by cisapride.

Table 4.1: Prescriptions of extramurally provided gastroprotectives (GPA's)

	Prescriptions (1=1,000)								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
GPA's (total)	3,328	3,662	3,969	4,242	4,352	4,607	4,820	5,196	7%
H₂ antagonists	1,539	1,770	1,850	1,860	1,766	1,729	1,631	1,535	0%
Proton-pump inhibitors	214	320	506	771	1,03	1,315	1,590	1,912	37%
Antacids	720	686	707	685	597	609	613	699	0%
Mucosa protectives	164	150	132	116	112	95	68	70	-11%
Eradication treatments	-	-	-	-	2	9	18	22	-
Other drugs	691	736	774	810	845	850	900	958	5%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

Development costs 1991-1998

Table 4.2 shows the costs for the use of the different GPA. In 1998, 700 million guilders (318 million Euros) were spent in the Netherlands on pharmacotherapy with drugs from this category. On average, the costs for GPA have increased 9% annually since 1991, although the rise in costs has been less high during the past five years and are about 6%. As expected, the highest increase in costs can be observed for the proton-pump inhibitors. For almost all other groups, a fall in costs is observed, which is much sharper during the last years than at the start.

Table 4.2: Costs of extramural supplied prescriptions of gastroprotectives (GPA's)

	Costs (1=1,000,000 guilders**)								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
GPA's (total)	389	473	534	588	633	628	648	700	9%
<i>H₂-antagonists</i>	240	276	307	306	290	237	193	168	-4%
<i>Proton-pump inhibitors</i>	79	118	155	204	268	316	380	450	29%
<i>Antacids</i>	15	18	12	15	8	8	7.5	9	-3%
<i>Mucosa protectives</i>	15	14	13	11	10	8	5	6	-11%
<i>Eradication treatments</i>	-	-	-	-	0.6	2.3	4.5	5	-
<i>Other drugs</i>	40	49	48	53	57	56	58	62	7%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]
** 1 Euro = 2.20371 Dutch guilders

4.4 Hospitals

Volume development 1991-1998

In Table 4.3 the volume development of acid-related admissions (inclusive treatments and consultations) in Dutch hospitals are shown for the period 1991-1998. Since 1991, the number of clinical admissions is decreasing an average of 1 % annually, while the number of day-treatments is increasing an average of 21% annually.

Table 4.3: Hospital admissions, hospital days, treatments and clinical consultations of patients with acid-related complaints as main diagnosis (ICD9CM: 530-537)

	Units (1=1,000)								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Hospital days	161	162	160	153	146	139	133	121	-4%
Admissions									
<i>Clinic</i>	12	12	13	12	12	12	12	11	-1%
<i>Day care</i>	0.9	1.2	1.8	2.1	2.6	2.8	3.1	3.2	21%
<i>Average hospital days</i>	12.5	11.9	11.2	10.6	10.2	9.5	9.1	8.7	-5%
Treatments									
<i>Endoscopy</i>	46	52	56	58	60	61	61	55	3%
<i>Biopsy</i>	17	16	20	20	16	18	20	21	4%
<i>Surgeries</i>	2.9	3.2	3.5	3.5	3.6	3.4	3.4	3.3	2%
<i>Others</i>	2.5	2.7	2.8	3.1	3.3	2.9	2.9	2.4	0%
Clinical consultations	18	19	19	20	19	19	19	17	-1%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

Since 1991, the number of hospital days has decreased about 4% annually. The number of treatments has increased about 3% annually, and the number of clinical consultation has remained practically unchanged in spite of a decrease in the number of hospital admissions.

Development costs 1991-1998

In 1998, 235 million guilders (107 million Euros)were spent for the treatment of acid-related disorders. Since 1991, these costs barely changed in spite of the shortened hospital stay and a decline in the number of admissions.

Table 4.4: Costs of admissions in general and academic hospitals for the treatment of acid-related disorders (ICD9CM:530-537)

		Costs (1=1,000,000 guilders ^{***})								
		1991	1992	1993	1994	1995	1996	1997	1998	V*
Hospital days										
	<i>Clinic</i>	133	136	136	135	129	126	123	114	-2%
	<i>Day care</i>	0.8	1.1	1.6	1.9	2.6	2.9	3.1	3.4	24%
Treatments										
	<i>Endoscopy</i>	65	72	78	81	84	86	84	76	2%
	<i>Biopsy</i>	23	23	28	28	23	25	27	29	4%
	<i>Surgeries</i>	4.2	4.2	4.1	4.0	3.8	3.5	3.7	3.5	-2%
	<i>Others</i>	2.3	2.5	2.5	2.9	3.1	2.7	2.6	2.4	1%
Clinical consultations**		4.9	4.9	5.1	5.2	5.4	5.1	5.7	5.5	2%
Total		233	244	255	258	251	251	249	235	0%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

** inclusive fee medical specialist for clinical treatment

*** 1 Euro = 2.20371 Dutch guilders

4.5 Development in number of users 1991-1998

In Table 4.5, the number of GPA users is shown in the period 1991-1998. Pursuantly, these were compared to a demographic projection based on data from 1991.

On basis of the growth so calculated, the number of users should have increased about 1% annually. In reality, the number of users increased 6% annually.

Table 4.5: Demographic development of the expected and observed number of patients using GPA's in The Netherlands.

	Users (1=1,000)							
	1991	1992	1993	1994	1995	1996	1997	1998
Expected**	1,089	1,103	1,117	1,129	1,140	1,150	1,160	1,167
V*	-	1%	1%	1%	1%	1%	1%	1%
Observed	1,089	1,160	1,234	1,306	1,317	1,376	1,459	1,549
V*	-	7%	6%	6%	1%	4%	6%	6%
Unexplained	0	57	117	177	177	226	299	382

* V: annual changes in percentage (method of calculation: year-(year-1)/(year-1)
** on basis of demography

As the above table shows, compared to 1991, there will be 380,000 more patients treated in 1998 than expected on basis of demographic estimates. This comes to about 30% of the present patient population that is undergoing pharmacotherapeutic treatment for acid-related disorders.

4.6 Specific factors

From the different analyses, it can be concluded that the increase in the use of GPA during the period 1991-1998 can be mainly explained by an increase in the number of treated patients. This increase is not to be explained by growth due to ageing of society, but apparently has other causes. A number of other relevant factors, which should then be considered, will be discussed below.

Helicobacter Pylori

Helicobacter Pylori (HP) is a major cause of ulcers and quite prevalent in The Netherlands. It is estimated that about 10-20% of the population is infected, and that the infection rate increases with age to 50% among the elderly. It is suspected that the elderly caught the infection long ago, and that in modern society the infection rate is much lower risk, resulting in a decrease of the number of HP-infections through the years [3-7]. This decline shall be accelerated by the eradication of HP. On that ground it, therefore, seems logical to assume that the use of, for example, proton-pump inhibitors will also decrease.

However, in our files we identified 525 patients that underwent an eradication treatment with omeprazol and a history and follow-up time of at least one year. In the year before the eradication treatment, 181 (34.5%) of the 525 patients used a proton-pump inhibitor. In the year following the eradication treatment, there remained 282 (53.7%) patients, of which 122 (23.4%) belonged to the chronic users. For more than 50% of the patients, the eradication treatment was the start of long-term use of a proton-pump inhibitor.

NSAIDs

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are used for a large number of diseases for indications like pain, inflammation, fever, or infection. Long-term use is observed in particular for patients suffering from rheumatic arthritis, osteoarthritis, or diseases associated with chronic pain or inflammation. It is a well-known fact that NSAIDs can cause gastrointestinal events. There are two reasons for this. The most common one is the inhibiting influence of NSAIDs on the formation of the enzyme cyclo-oxygenase (COX) and by that on the formation of prostaglandines. This causes a shortage of prostaglandines, agents that shield the stomach wall against the penetrating effects of acid. The second reason is that most NSAIDs are weak acids that do not dissolve in the stomach, but penetrate the cell by which intracellular reactions can appear with mucosa damage as result [8]. The use of NSAIDs can influence the use of GPA in two different ways: 1) by causing gastrointestinal events followed by the use of GPA (NSAIDs-induced), and 2) in the prevention of gastrointestinal events by simultaneous use of GPA (NSAIDs-prevention). Both methods of interference have been studied more in detail.

a. GPA-use as a result of NSAIDs damage

The damage that can be caused by those NSAIDs can be calculated on basis of the prevalence of use of NSAIDs and the relative risk of the occurrence of gastrointestinal events, by estimation of the population attributive risk (PAR). The point prevalence of the use of NSAIDs has been measured in PHARMO and has increased from 2.3% in 1991 to 3% in 1998. Also abroad, these prevalences are measured [9]. The relative risk is determined in various manners and in different countries. In more recent studies and a yet to be published study by the PHARMO Institute for the situation in The Netherlands, we observed on average a relative risk, varying from 2.5-8 [9-11]. Table 4.6 is based on a relative risk of 5.0 and prevalences such as have been measured in PHARMO. In 1998, 10.6% of GPA-use could be attributed to NSAID-induced gastrointestinal events.

Table 4.6: Estimate of the use of GPA in relation to the use of NSAIDs

	1991	1992	1993	1994	1995	1996	1997	1998
GPA prescriptions (total, 1 = 1,000)	3,328	3,662	3,969	4,242	4,352	4,607	4,820	5,196
NSAIDs-induced	8.4%	7.1%	7.7%	8.8%	8.1%	10.5%	10.9%	10.6%
NSAIDs-prevention	3.0%	4.5%	5.9%	7.4%	9.0%	10.9%	13.3%	15.9%
Total NSAIDs related	11.4%	11.6%	13.6%	16.2%	17.1%	21.4%	24.2%	26.5%
Expressed in GPA prescriptions	379	425	540	687	744	986	1,166	1,377

b. GPA-use in prevention of NSAIDs damage

The preventive use of GPA with NSAIDs use has been studied in two different ways. Primary preventive use refers to patients who use NSAIDs and GPA for the first time and simultaneously. This means that these persons do not have a history of medical treatment for gastrointestinal events. The second group consists of patients who get NSAIDs and GPA prescribed on the same prescription while in the month preceding the prescription, no treatment with GPA can be observed. All patients from this group do have a history of GPA treatment. The GPA prescriptions of the above-mentioned two patient groups are designated to primary and secondary prevention of gastrointestinal events, respectively. More than 80% of GPA prescriptions in 1998 were issued for secondary prevention, that is for patients with ulcers and a history of gastrointestinal events in the anamnesis [8]. In most of the cases, proton-pump inhibitor were the most preferred antacids.

4.7 conclusions

In the preceding paragraphs, a number of studies have been presented regarding the pharmacotherapy of acid-related diseases, as well as a survey of the involved hospital admissions. The total costs of these drug therapies and hospital expenditures came to circa one billion guilders (454 million Euros) in 1998, of which 700 million guilders (318 million Euros) were for pharmacotherapy.

In summary, the following conclusions:

- In the period 1991-1998, there is an average increase in volume-and costs in the use of GPA of 7%, respectively 9%, an increase that can only be partially explained by the ageing of society.

To place these developments in the right context, it is important to take into account the following:

1. In practice, HP-eradication treatments (in more than 50% of the cases) are followed by the use of proton-pump inhibitors. With the increased attention for HP-eradications, the HP-induced use of proton-pump inhibitors shall probably increase in the future.
 2. The significance of the increased use of NSAIDs; specifically, the preventive prescription of gastroprotectives has been propagated in medical literature for the last years.
- During that same period, the directly acid-related hospital admissions decreased on average 1% annually with a decrease in the number of hospital days of 4%, with costs remaining the same.

4.8 Literature

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5 DIABETES MELLITUS

5.1 Background

Diabetes mellitus is a disease with a high prevalence. According to an epidemiological population survey, about 440,000 people in The Netherlands suffer from some type of diabetes mellitus. The prevalence among women is slightly higher than in men [1]. The classification of diabetes mellitus has recently been revised and has significant consequences for diagnostics and treatment.

Diabetes mellitus type 1 is the form known as insulin-dependent diabetes. Diabetes type 2, also known as adult-onset diabetes, is characterized by an increased level of blood glucose from lack of insulin production by the pancreas and/or impaired glucose absorption by the body cells (insulin-resistance). Especially, in cases of patients suffering from diabetes mellitus type 2, underdiagnosis takes place, with estimates increasing up to 50% of patients that have not been diagnosed as such. The treatment of this type of diabetes usually starts with food and diet advices, followed by a treatment with oral glucose-lowering medication. In those cases where oral drugs do not generate enough effect, treatment with insulin follows.

The goal in the treatment of diabetes is the normalization of the glucose level. Based on several large studies of which the results became known during the last few years, an intensive treatment with a strict management of the insulin dosage is recommended to prevent, or postpone long-term complications [2,3]. These include both microvascular complications (eye, kidney, and nerve diseases) and macrovascular diseases (angina pectoris, heart infarct). A possible risk with a rigorous management of the glucose level is an increased risk of the occurrence of hypoglycaemia. Therefore, good self-control and monitoring are essential. It is not without reason that in the treatment of diabetes, many multi-disciplinary initiatives have been developed in the field of integral, transmural care and disease management.

It is becoming clearer that diabetes is not an isolated disease, but often goes hand in hand with cardiovascular diseases, obesity, etc. The burden of care and the economic consequences of this co-morbidity for diabetes mellitus is significant [4,5].

5.2 Selection of patients

To study the pharmacotherapeutic development of diabetes, patients have been selected on the basis of the use of insulin or oral glucose-lowering drugs. These drugs are defined into ATC-group A10 (A10A: insulins, A10B: oral anti-diabetics).

Patients have been selected for study if they have used at least once a medication from this group in the year of study. Thereupon, all hospital admissions in The Netherlands have been selected, in

imitation of Polder et al. [7], with as main diagnoses: ICD-codes 250-251. Both ICD-codes refer to disorders of the glucose-level among which hyperglycemia, hypoglycemia and related diseases. For these patients, the volume and costs of the use of insulin and oral glucose-lowering drugs has been explored in the period 1991-1998. Also, the number of hospital admissions and the related costs have been marked down.

5.3 Drugs

Development volume 1991-1998

Table 5.1 shows the development in the total number of prescriptions for oral glucose-lowering drugs in The Netherlands for the period 1991-1998. Since 1991, the use has increased by an average of 8% annually. Outstanding is the increase of the short-acting insulins. The highest rise in volume, however, is to be seen in the use of the oral glucose-lowering drugs. The use of biguanides, nearly exclusively metformin, has tripled since 1991. The use of metformin is recommended for those patients that do not get sufficient results when using a current sulphonylureas derivative, especially for persons with obesity [5]. The increase in the use of metformin is seen in relation to a rising prevalence and recognition of the risks of obesity [1]. Obesity is one of the major risk factors of diabetes type 2 and thereby contributes greatly to the high costs of care for this disease [4].

Table 5.1. Prescriptions of extramurally supplied oral glucose-lowering drugs									
	Prescriptions (1=1,000)								
	1991	1992	1993	1994	1995	1996	1997	1998	V*
Anti-diabetics (total)	1,798	2,016	2,153	2,259	2,311	2,510	2,696	3,151	8%
Insulins	753	810	843	826	818	869	925	1,062	5%
Short-acting	152	165	183	189	196	209	217	246	7%
Insulin-analogues	-	-	-	-	-	5	28	64	-
Intermediate	166	177	180	168	164	175	192	223	5%
Short + Intermediate	432	465	478	467	456	478	486	528	3%
Long acting	3	3	2	2	2	2	2	1	-12%
Oral anti-diabetics	1,045	1,206	1,310	1,433	1,493	1,641	1,771	2,089	10%
Sulphonylureum derivates	856	961	1,025	1,093	1,124	1,193	1,262	1,494	8%
Biguanides	171	219	252	304	326	388	444	538	18%
Alpha-glucosidase inhibitors	18	26	33	36	43	60	65	57	19%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

Development costs 1991-1998

Table 5.2 shows the costs of the use of oral glucose-lowering drugs during the period 1991-1998. In 1998, these costs came to about 275 million guilders (124 million Euros).

Table 5.2: Costs of extramurally supplied drugs for the treatment of diabetes mellitus									
	Costs(1=1,000.000 guilders**)								
	1991	1992	1993	1994	1995	1996	1997	1998	V*
Anti-diabetics (total)	159	182	207	224	220	208	227	275	8%
Insulins	105	122	146	156	150	146	159	188	9%
Short-acting	22	27	32	37	38	39	41	47	12%
Insulin-analogues	-	-	-	-	-	0.5	3.9	10.2	-
Intermediate	21	21	27	27	25	26	28	33	7%
Short + Intermediate	62	74	87	92	87	80	86	98	7%
Long acting	0.4	0.4	0.3	0.3	0.2	0.1	0.1	0.1	-15%
Oral anti-diabetics	54	60	61	68	70	62	68	87	8%
Sulphonylureum derivates	47	50	51	54	55	47	51	67	6%
Biguanides	6	8	7	11	12	11	13	16	17%
Alpha-glucosidase inhibitors	1	2	3	3	3	4	4	4	26%

* V: average annual change in the period 1991-1998! [calculation method: S(annual changes in terms of percentage)/n]

** 1 Euro = 2.20371 Dutch guilders

5.4 Hospitals

Development volume 1991-1998

Table 5.3 shows the volume development of diabetic-related hospital admissions (including treatments and consultations) in The Netherlands for the period 1991-1998. Contrary to the considerable increase in volume of the use of drugs, the number of clinical admissions decreases 3% and the number of hospital days 4% annually. One can see that there is a distinct trend in less often admitting patients with diabetes mellitus to hospital.

Table 5.3: Hospital admissions, admission days, treatment and clinical consultations of patients with diabetes mellitus as main diagnosis (ICD9CM: 250-251)

	Units (1=1,000)								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Hospital days	290	276	281	258	244	234	218	210	-4%
Admissions									
Day care	0.2	0.3	0.9	0.8	0.9	1.1	0.8	0.7	33%
Clinic	17.6	17.1	17.6	17.2	16.2	15.9	15.3	14.6	-3%
Average hospital days	16.3	15.9	15.2	14.3	14.3	13.8	13.5	13.7	-2%
Treatments	5.0	4.9	5.5	5.7	5.4	5.2	5.4	4.8	0%
Clinical consultations	26.8	26.4	27.8	26.9	25.9	25.4	24.2	22.7	-2%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

Development costs 1991-1998

In 1998, 212 million guilders (96 million Euros) were spent on admissions in the combined Dutch hospitals (including treatments and consultations) on patients with diabetes mellitus. These costs can be compared to the estimates of Polder et al. [7]. For the correct interpretation of those figures, it is important to realize that these only refer to admissions that are directly related to diabetes and not to the cardio-vascular, neurological and nephrological complications of the disease in the long term. Therefore, it is also plausible that it is an underestimation of the total treatment costs of patients with diabetes mellitus in hospitals.

Table 5.4: Costs of admissions in general and academic hospitals for the treatment of diabetes mellitus (ICD9CM: 250-251)

	Costs (1=1,000,000 guilders ^{***})								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Hospital days	249	240	251	236	226	219	208	206	-3%
Day care	0.2	0.2	0.8	0.8	0.8	1.1	0.8	0.7	43%
Clinic	249	240	250	235	225	218	207	205	-3%
Treatments	4.0	3.8	4.3	4.5	4.3	4.4	4.5	4.3	1%
Clinical consultations**	1.8	1.7	1.8	1.8	1.7	1.7	1.6	1.5	-2%
Total	255	246	257	243	232	225	215	212	-3%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]
** inclusive fee medical specialist for clinical treatment
*** 1 Euro = 2,20371 Dutch guilders

5.5 Development in number of users 1991-1998

In Table 5.5, the development in the number of glucose-lowering agents is shown. From the table, it is clear that the demographic developments only contribute a fraction (about 1% annually) to the observed growth of the number of patients being treated for diabetes mellitus. The real increase in the number of patients amounted to 6% annually. In 1998, over 120,000 more patients were treated than in 1991. This covers about 30% of the current patient population with diabetes mellitus.

Table 5.5: Demographic development in the expected and observed number of patients that use glucose- lowering drugs

	Users (1=1,000)							
	1991	1992	1993	1994	1995	1996	1997	1998
Expected**	248	252	256	259	262	265	268	271
V*	-	2%	2%	1%	1%	1%	1%	1%
Observed	248	262	276	295	307	323	344	371
V*	-	6%	5%	7%	4%	5%	7%	8%
Unexplained	0	11	21	36	45	57	76	100

* V: annual changes in percentage (method of calculation: year-(year-1)/(year-1)
** on basis of demography

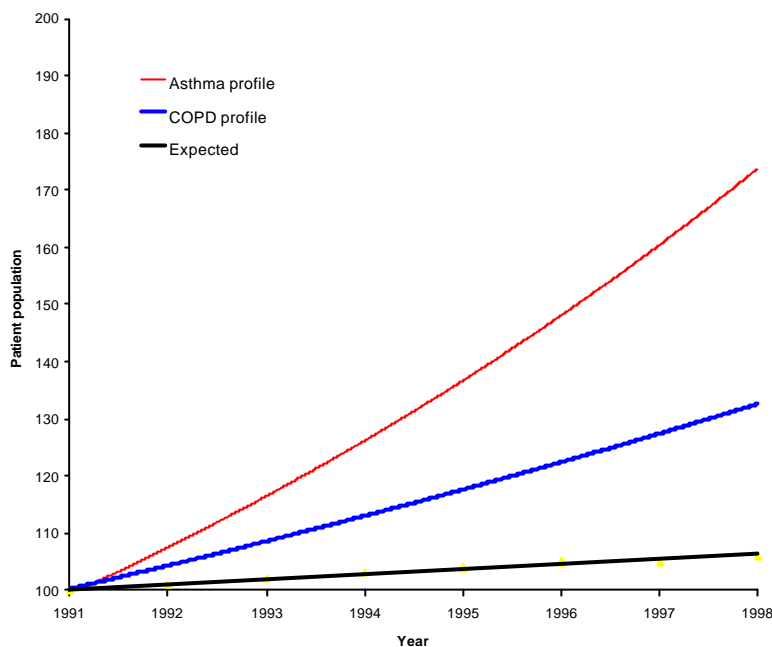
5.6 Specific factors

It can be concluded from the different analyses that the increase in use of glucose-lowering drugs during the period 1991-1998 can be explained by the increase in number of treated patients. This increase can hardly be explained by growth and ageing but has apparently other causes. A number of relevant factors which then could be considered, will be discussed in more detail.

Observed Increase

To obtain more insight into the increase in number of patients with anti-diabetics medication, patients using at least two different drug prescriptions for glucose-lowering agents, have been classified into two different groups. Patients that at any time during the period 1991-1998 were treated with an oral glucose-lowering agent have been classified as diabetes mellitus type 2 patients. All other patients have been classified as diabetes mellitus type 1 patients. Figure 5 shows the percentual growth of both groups. In both groups a higher rise took place than expected, with the greatest increase in patients with diabetes mellitus type 2.

Figure 5.1: Development in number of patients with a user's profile of type 1, or type 2 diabetes mellitus, and the expected growth by demographic changes in the period 1991-1998 (index-basis 1991=100)



In literature, several reasons are given that could help explain the observed growth. Firstly, there are indications that in the last few decades, the prevalence of both diabetes type 1 and diabetes type 2 is increasing [1]. The increase in the occurrence of obesity is seen in relation to the increase of diabetes type 2 [5].

Intensity in research and treatment

The increase in the number of treated patients needs to be considered in the perspective of a more intensive research and diagnostics. The number of medically treated diabetics seems to grow faster than the prevalence of the disease. According to a population survey, there were about 400,000 patients suffering from diabetes in The Netherlands in 1994 [1].

According to the results of this study, there were about 300,000 patients treated with glucose-lowering agents in that same year, which comes down to 75% of all patients with diabetes.

The costs involved in the use of insulin pens, glucose-measurement devices, strips and additional accessories have increased from 28 million guilders (13 million Euros) in 1991 to 105 million guilders (48 million Euros) in 1998. Apparently, next to more intensive care, self-treatment/and-control also play a role that is becoming more and more important.

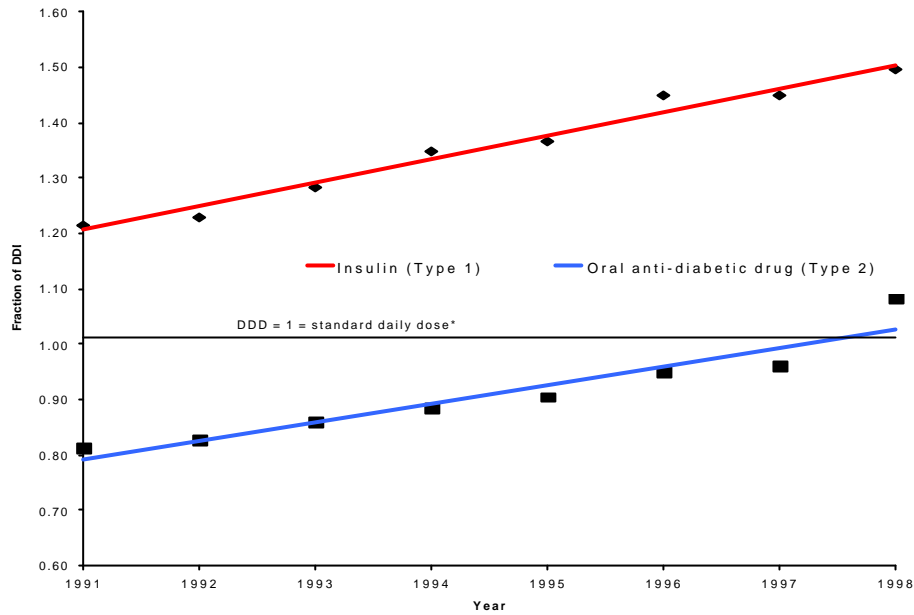


Figure 5.2 shows the mean prescribed daily dose represented in fractions of the DDD. A clear rise can be observed in the daily prescribed dose through the years, which is in line with the present therapeutic insights to put patients with diabetes as rigorously as possible on medication to prevent long-term complications [2,3].

Complications and co-morbidity

The prevention of complications in diabetes mellitus is becoming more and more important through the years. A more intensive treatment of diabetes seeks to prevent these complications. Various publications have indicated that the costs for treatment of complications related to diabetes could exceed the immediate costs of treatment many times [9-12]. Table 5.6 shows the medical costs for the treatment of cardiovascular diseases both in patients with diabetes, and in a control group of similar size and composition. Next to the treatment with glucose-lowering agents, the costs for the co-medication of patients with diabetes add up to circa 600 million guilders (272 million euros) annually. For cardiovascular diseases, these costs amount to circa 195 million guilders (88 million euros) annually, three times as much as for non-diabetics. The most striking feature is that the cost development for patients with diabetes rises more strongly compared to a control group of patients without diabetes. The costs for drugs that are used for cardiovascular disorders in patients with diabetes increase 14% annually against 11% for control patients. The most important groups representing extra costs and the highest rise in time, are the hyperlipemics and the ACE-inhibitors. For both groups of drugs, there exists extensive evidence concerning the favourable therapeutic effect in patients with diabetes.

Table 5.6: Costs co-medication for diabetics compared with non-diabetics

		Costs (1=1,000,000 guilders****)								
		1991	1992	1993	1994	1995	1996	1997	1998	V*
Cardiovascular	Diab	78.3	90.3	106.9	118.5	129.1	126.7	155.0	195.6	14%
	Contr	30.6	34.0	38.5	40.9	42.1	36.6	49.5	61.4	11%
	Ratio	2.6	2.7	2.8	2.9	3.1	3.5	3.1	3.2	
Hyperlipaemica	Diab	0.4	0.4	1.1	1.5	2.4	13.6	32.2	48.8	132%
	Contr	0.1	0.0	0.1	0.2	0.3	3.9	10.5	14.2	229%
	Ratio	4.5	9.0	7.1	7.4	9.1	3.5	3.1	3.4	
ACE –inhibitors	Diab	18.9	22.2	28.6	34.0	38.4	37.6	38.9	48.3	13%
	Contr	6.2	6.7	8.7	9.8	10.3	8.9	10.8	13.7	13%
	Ratio	3.0	3.3	3.3	3.5	3.7	4.2	3.6	3.5	
Ca-antagonists	Diab	13.9	18.2	23.4	26.1	28.0	22.5	21.7	26.7	11%
	Contr	5.7	7.1	8.6	9.0	9.5	6.9	7.4	9.4	9%
	Ratio	2.4	2.6	2.7	2.9	2.9	3.3	2.9	2.8	
Others**	Diab	45.1	49.6	53.9	56.9	60.3	53	62.2	71.8	7%
	Contr	18.6	20.2	21.0	21.9	22.0	16.9	20.8	24.1	5%
	Ratio	2.4	2.5	2.6	2.6	2.7	3.1	3.0	3.0	
Other medication***	Diab	201.3	232.1	271.4	304.4	336.6	322.1	362.2	406.5	11%
	Contr	100.8	109.5	130.8	137.3	144.7	128.5	153.3	172.3	8%
	Ratio	2.0	2.1	2.1	2.2	2.3	2.5	2.4	2.4	
Total	Diab	279.6	322.4	378.3	422.9	465.7	448.8	517.2	602.2	12%
	Contr	131.5	143.5	169.2	178.2	186.8	165.1	202.7	233.7	9%
	Ratio	2.1	2.2	2.2	2.4	2.5	2.7	2.6	2.6	

* V: mean annual change during the period 1991-1998 [calculation method: $S(\text{annual changes on percentage})/n$]

** other cardiovascular medication, among which nitrates, digoxins, diuretics

*** all other medication such as for instance antibiotics, agents for use in ophthalmology

**** 1 Euro = 2.20371 Dutch guilders

5.7 Conclusions

In the preceding paragraphs a number of macro surveys have been presented regarding the pharmacotherapy of diabetes mellitus, together with an overview of the hospital admissions related to diabetes. The costs of treatment with glucose-lowering drugs together with the costs of hospital treatments add up to circa 500 million guilders (227 million Euros) annually. This amount is probably an underestimation. In summary, the following conclusions:

- During the period 1991-1998, there is an average annual volume- and cost increase of 8% in the use of glucose- lowering drugs, an increase that can only be partly contributed to the ageing of the population. To place these developments in the right context, it is important to take into account the following:
 1. an autonomous increase in the prevalence of diabetes, by which the increase in obesity is an important factor.
 2. a more intensive detection and diagnostics of diabetes and a clear realization that diabetes is an important risk factor for morbidity and mortality. This development is also consistent with the discovered increase in the number of treated patients of 6% annually.
 3. A more intensive treatment of the patient with diabetes and in accordance with the actual therapeutic insights, preferably, a tighter regimen of medication, as well as in most cases, a higher dose in order to prevent long-term complications.
- In the same period, the directly to diabetics-related hospitalization decreased an average of 3% annually, with a decrease in the number of hospital days of 4% annually, which is clearly a result of the extramuralisation, which is taking place.
- The discovered developments in pharmacotherapy of cardiovascular co-morbidity are consistent with the awareness that diabetes is a major risk factor for serious cardiovascular complications (heart infarct, stroke), and that medical treatment of hypertension and of a raised cholesterol level are indicated.

5.8 Literature

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6 ASTHMA AND COPD

6.1 Background

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are both chronic obstructive respiratory inflammations. Asthma is a chronic disease with symptoms as a wheezing breath, shortness of breath, and coughing with periods of exacerbation which depending on nature and seriousness are described as asthma attacks or asthma exacerbations. With asthma, there is a local inflammation of the respiratory tract, which plays an important role in the bronchial hyper-reactivity. Also, asthma often has an allergic background. The disease manifests itself commonly at a young age; and, in first instance, is usually not recognized as such.

COPD partly resembles asthma as regards symptomatology; and in practice, it is sometimes hard to distinguish between these two diseases, especially within the elderly. Usually, the disease only occurs after the 50th year of one's life and is characterized by shortness of breath in first instance manifesting itself with exertion, later also when at rest. COPD is differentiated in chronic bronchitis and emphysema. It is generally accepted that smoking plays a major part in the occurrence of COPD [1]. According to figures of the RIVM, at least 175,000 patients should be suffering from asthma and 290,000 of COPD. More recent estimates show even higher figures, and there are indications that the incidence of both asthma and COPD is increasing [2]. For COPD, this is not in the least due to the fact that smokers from the past, through ageing, are now coming in the high-risk period.

The pharmacotherapy of both diseases has changed immensely during the past decade. During the seventies and eighties, the emphasis was on bronchodilatation, while during the last ten years, the intensive and chronic treatment of inflammation is emphasized [3,4]. International guidelines do emphasize the latter, by which the use of inhalation corticosteroids have become the fundament on which other forms of pharmacotherapy are added [5-7]. Patients have medication in order to both treat and prevent attacks which, depending of the seriousness of the disease, is little by little being built up. Therefore, polytherapy is usual. Recently added to the assortment of medication are the long-acting β -antagonists. Their effect is based on bronchodilatation and possibly also to treat the underlying inflammation. The long-acting β -antagonists are used for the maintenance treatment of asthma and COPD.

6.2 Selection of patients

For the study of the development of the pharmacotherapy of asthma and COPD, patients have been selected on basis of the drug use registered for these indications [8]. These are drugs that are classified in ATC-group R03. Patients have been selected for study if they used in the year of the study, at least once, a drug from this group. Also, the use of oral glucocorticoids, antihistamines

and cough medication by these patients has been identified. These drugs are, after all, also used in the treatment of asthma and COPD. Pursuantly, all hospital admissions in The Netherlands have been selected having as main diagnosis: ICD-codes 490-496. Both ICD-codes refer to admissions with chronic obstructive lung diseases as main diagnosis among which asthma and COPD. The volume and costs of the use of pharmacotherapy have then been identified for the period 1991-1998. The number of hospital admissions and the relevant costs have also been recorded.

6.3 Drugs

Development of volume 1991-1998

Table 6.1 shows the development of the number of prescriptions for asthma and COPD drugs in The Netherlands for the period 1991-1998. Since 1991, there has been an average increase in use of 7% annually. The groups of drugs showing the highest increase are the inhalation corticosteroids, the parasympatolytics, the systemically administered corticosteroids, and the long-acting β -agonists. These agents are predominantly prescribed as maintenance therapy. The cromoglycates, xanthines and the systemic β -antagonists seem to abandon the field.

Table 6.1: Prescriptions of extramurally dispensed asthma and COPD-drugs

	Prescriptions (1=1,000)								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Asthma and COPD drugs	4,788	5,158	5,526	5,816	6,105	6,343	6,701	7,501	7%
<i>Long-acting β-antagonists</i>		34	158	254	352	436	571	645	-
<i>Short-acting β-antagonists</i>	1,562	1,631	1,645	1,709	1,756	1,812	1,908	2,206	5%
<i>Cromoglicates</i>	184	182	191	185	143	123	100	72	-12%
<i>Inhalation corticosteroids</i>	923	1,108	1,355	1,576	1,763	1,899	2,104	2,278	14%
<i>Mucolytics</i>	531	567	625	494	542	434	338	334	-5%
<i>Parasympatolytics</i>	447	504	541	637	685	785	861	1,019	13%
<i>Systemic corticosteroids</i>	311	353	364	384	382	437	468	565	9%
<i>Systemic β-antagonists</i>	346	314	270	249	199	156	122	147	-11%
<i>Xanthines</i>	484	465	377	328	283	261	229	235	-10%
Other drugs**	1,115	1,153	1,316	1,042	1,087	1,180	1,216	1,389	4%
<i>Antihistaminics</i>	424	472	519	485	500	527	534	580	5%
<i>cold medicines</i>	358	384	463	367	401	446	470	513	6%
<i>cough and cold medicines</i>	333	297	334	190	186	207	212	296	1%
Total	5,903	6,311	6,842	6,858	7,192	7,523	7,917	8,890	6%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

** ATC code: Glucocorticoids: H02BA; Antihistaminics: R06A; Cold medicine: R01A; and Cough and cold medicines: R05.

Development costs 1991-1998

The costs of pharmacotherapy in the treatment of asthma and COPD are for a large part determined by the inhalation corticosteroids and the long- and short-acting β -antagonists. In 1998, they encompass more than 70% of the costs in this group of drugs. Both the costs and the number of prescriptions in the different years agree with the data from the GIP [9].

Table 6.2: Costs of extramurally dispensed asthma and COPD drugs

	Costs (1 = 1,000,000 guilders ^{***})								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Asthma and COPD drugs	313	351	408	449	482	518	534	556	9%
<i>Long-acting β-antagonists</i>	-	5	29	49	66	91	90	90	-
<i>Short-acting β-antagonists</i>	100	101	101	97	94	94	89	103	1%
<i>Cromoglicates</i>	21	21	24	23	17	14	9	6	-15%
<i>Inhalation corticosteroids</i>	100	122	154	180	198	207	230	236	13%
<i>Mucolytics</i>	22	25	26	23	29	29	28	25	3%
<i>Parasympaticolytics</i>	36	41	43	49	54	60	65	74	11%
<i>Systemic corticosteroids</i>	5	7	7	7	7	8	10	10	11%
<i>Systemic β-antagonists</i>	10	10	8	7	5	4	3	3	-15%
<i>Xanthines</i>	19	19	16	14	12	11	10	9	-10%
Other drugs**	41	32	37	35	38	40	42	49	3%
<i>Antihistaminics</i>	15	16	17	17	17	18	19	22	6%
<i>cold medicines</i>	11	12	15	15	18	19	20	23	11%
<i>cough and cold medicines</i>	15	5	5	3	3	3	3	4	-10%
Total	354	384	445	484	520	558	576	605	8%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

** ATC code: Glucocorticoids: H02BA; Antihistaminics: R06A; Cold medicine: R01A; and Cough and cold medicines: R05.

*** 1 Euro = 2.20371 Dutch guilders

6.4 Hospitals

Development of volume 1991-1998

Table 6.3 shows the volume development of hospital admissions related to asthma and COPD (treatments and consultations, inclusive) in Dutch hospitals for the period 1991-1998. The number of hospital admissions for asthma and COPD shows a 2% average annual increase over the studied time period. The average hospital stay, however, decreases from 15.3 days in 1991 to 13.3 days in

1998. Except for a slight shift to the day care, the different key numbers have hardly changed through the years.

Table 6.3: Hospital admissions, hospital days, treatments and clinical consultations of patients with asthma and COPD as main diagnosis (ICD9CM; 490-496)

	Units (1=1,000)								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Number of admissions	27	27	30	29	30	30	30	31	2%
COPD (ICD 491,492,496)	20.2	20.5	22.1	21.5	22.3	22.5	22.8	23.3	2%
Asthma (ICD 493)	5.6	5.6	6.1	5.9	6.0	6.1	5.8	6.6	3%
Others (ICD 490,494,495)	1.4	1.3	1.6	1.5	1.4	1.3	1.2	1.3	0%
Hospital days	413	415	434	418	418	416	408	413	0%
Day care	1.1	1.3	1.3	1.2	1.2	1.5	1.4	1.5	5%
Clinic	411	414	432	417	416	414	407	412	0%
Average Hospital stay	15.3	15.4	14.5	14.4	13.9	13.9	13.6	13.3	-2%
Treatments	4.0	4.1	4.4	4.1	4.0	4.0	4.1	4.1	0%
Clinical consultations	36.6	37.0	40.1	39.3	40.2	40.1	39.7	41.4	2%

V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage})/n$]

Cost Development 1991-1998

In 1998, the collective Dutch hospitals spent more than 400 million guilders (182 million Euros) on the treatment of asthma and COPD and related syndromes. The raise in costs that can be observed in hospitals amounts to circa 2% annually.

Table 6.4: Costs of admissions in general and academic hospitals for the treatment of asthma and COPD (ICD9CM: 490-496)

	Costs (1=1,000,000 guilders ^{***})								V*
	1991	1992	1993	1994	1995	1996	1997	1998	
Hospital days	358	367	393	385	395	401	395	410	2%
Day care	357	366	392	384	390	396	394	409	2%
Clinic	1	1.2	1.1	1	1.2	1.5	1.4	1.5	7%
Treatments	2.2	1.9	2	2.3	2.1	2.2	2.2	2.2	0%
Clinical consultations	1.4	1.2	1.3	1.4	1.4	1.3	1.5	1.6	2%
Total	362	370	396	389	395	401	399	414	2%

* V: average annual change in the period 1991-1998 [calculation method: $S(\text{annual changes in terms of percentage}/n)$
** inclusive fee medical specialist for clinical treatment
*** 1 Euro = 2,20371 Dutch guilders

6.5 Development in number of users 1991-1998

Table 6.5 shows the development of the number of users of asthma and COPD- agents over the period 1991-1998. From the table, it is clear that the demographic developments only contribute a fraction (circa 1% annually) to the true increase in the number of patients being treated for asthma and COPD. The increase in the number of patients came to more than 7% annually. In 1998, almost a half million patients more than in 1991 were treated, a much greater increase than could have been expected on the basis of demographic developments.

Table 6.5: Demographic development of the expected and observed number of patient using drugs for asthma and COPD in The Netherlands

	Users (1=1,000)							
	1991	1992	1993	1994	1995	1996	1997	1998
Expected**	727	735	742	749	755	761	767	773
V*	-	1%	1%	1%	1%	1%	1%	1%
Observed	727	771	843	910	948	998	1,106	1.2
V*	-	6%	9%	8%	4%	5%	11%	8%
Unexplained	0	36	101	161	193	237	339	427

* V: annual changes in percentage (method of calculation: year-(year-1)/(year-1))
 ** on basis of demography

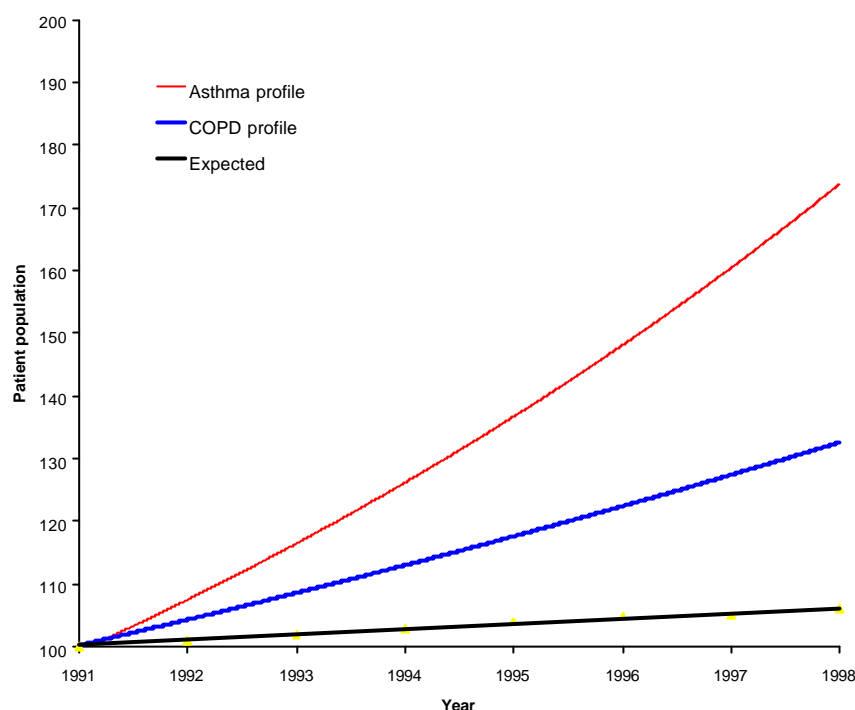
6.6 Specific factors

From the different analyses it can be concluded that the increase in the use of asthma and COPD agents in the period 1991-1998 is to a great extent caused by the increase in the number of treated patients. This increase is hardly explained by demographic developments, but apparently has other causes. A number of relevant factors which should then be thought of will be discussed below.

Autonomous growth

To obtain more insight into the development of asthma and COPD- drug use for asthma and COPD separately, the patients have been divided into two groups. The condition to be included in this analysis was that patients were dispensed at least two prescriptions for asthma and COPD-drugs per year. Patients with an asthma profile were under the age of 50, patients with a COPD-profile were 50 years of age or older.

Figure 6.1: Development in the number of patients with a user's profile of asthma or COPD, and the expected growth through demographic changes in the period 1991-1998. (index-basis 1991 = 100)



The increase of the number of patients with a user's profile of asthma or COPD in the period 1991-1998 is shown in Figure 6.1. A curve of an expected increase based on demographic developments is also added. It is obvious that with respect to both profiles a strong increase has taken place with the highest increase for patients with an asthma-profile. The number of patients with a user's profile of asthma came to circa 260,000 in 1994, and the number of patients with a user's profile of COPD amounted to circa 270,000. The latter number is very similar to the estimated number of COPD-patients in 1994 on the basis of general practitioners' registrations [1].

The increase in the number of patients that use asthma and COPD-medication is only partly reflected by data about hospital admissions. As presented in Table 6.3, both the admissions for asthma and for COPD did increase 3% respectively 2% annually in the observation period, significantly less than the 9% increase of the number of users of medication.

Intensity of detection and treatment

Table 6.6 shows per group the percentage of users of asthma and COPD medication. From the data in this table it becomes clear that in 1998 at least 60% of all patients used inhalation corticosteroids. In 1991, this percentage was only 40%. This raise is consistent with the changed therapeutic insights that emphasise since the mid-nineties the use of these agents and represents a clear trend towards more intensive care for these patients [5,6].

Table 6.6: Percentage of users of the different asthma and COPD medication

<i>Asthma and COPD drugs*</i>	1991	1992	1993	1994	1995	1996	1997	1998
	%	%	%	%	%	%	%	%
<i>Long-acting β-antagonists</i>	0	2	5	7	9	11	13	13
<i>Short-acting β-antagonists</i>	61	60	60	59	59	59	59	62
<i>Cromoglicates</i>	8	8	8	7	6	5	3	2
<i>Inhalation corticosteroids</i>	41	47	53	56	59	61	62	60
<i>Mucolytics</i>	29	29	30	20	21	16	11	10
<i>Parasympaticolytics</i>	17	18	17	19	19	21	21	20
<i>Systemic corticosteroids</i>	16	16	17	16	16	17	16	18
<i>Systemic β-antagonists</i>	20	18	15	13	10	8	5	5
<i>Xanthines</i>	19	16	11	8	7	6	5	4

** Percentages total up to more than 100%, because patients can use different drugs simultaneously.*

The 7% annual growth in the number of users of asthma and COPD agents can hardly be explained by an increase in the number of patients with light forms of respiratory tract problems for which, incidentally, a short acting β -agonist is usually given. Of all patients, more than 60% used a short-acting β -agonist in 1991. This percentage remained practically constant over the years, as well as the total cost for the use of these drugs.

6.7 Conclusions

In the preceding paragraphs a number of macro-studies have been presented regarding the pharmacotherapy of asthma and COPD, as well as an overview of the hospital admissions related to these diseases. The costs of treatments using asthma and COPD drugs and the treatment costs in the hospital went over one billion guilders (450 million Euros) in 1998. This amount is probably an underestimation in which, for example, morbidity related to COPD, such as serious heart failing, has not been included. In summary, the following conclusions:

- In the period 1991-1998, an average volume- and cost increase in the use of asthma and COPD drugs was observed of 7% and 9%, an increase which can only be partly related to ageing of the population. To place these developments in the right context, it is important to take into account the following:

1. an autonomous increase in the prevalence of asthma and COPD, in which with respect to the latter, smoking is an important factor. Especially in children, the prevalence of asthma is growing.
 2. the recognition that asthma, in any case, can be treated adequately with pharmacotherapy. The use of drugs in the treatment of COPD is clearly still in development. This is also consistent with the found annual increase of 7% in the number of treated patients.
 3. A more intensive treatment of the inflammation process with inhalation corticosteroids corroborates with the present therapeutic insights in order to treat inflammation and henceforward prevent exacerbations. Nevertheless, the average costs for pharmacotherapy per patient do remain rather constant at about 500 guilders (227 Euros) per year.
- In the same period, the directly to asthma and COPD-related hospitalizations increased on average 2% annually, while the number of hospital days did remain constant.

6.8 Literature

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7 LIST WITH ABBREVIATIONS

ATC	Anatomic(al) Therapeutic(al) Chemic(al) code (WHO standard)
BTW	VAT= Value Added Tax
CBS	Central Bureau of Statistics
CBV	Foundation CBV: in charge of coding hospital procedure tariffs
COPD	Chronic Obstructive Pulmonary Disease
CTG	Central Authority concerning Tariffs in Health Care
CVV	Dutch coding system for coding of procedures in hospitals
CVZ	Health Care Insurance Council
DDD	Defined Daily Dose (WHO standard)
DDDeq	Fraction of the DDD used per day
HP	Helicobacter Pylori
ICD	International Classification of Diseases
iMTA	Institute for Medical Technology Assessment
GPA	Gastroprotectives, drugs for acid-related diseases
GIP	Drugs Information Project
JOZ	Annual Care Report
KNMG	The Royal Dutch Association for the advancement of Medicine
KNMP	The Royal Dutch Association for Advancement of Pharmacy
LMR	The Dutch National Medical Registration
NEFARMA	Dutch Association of the Research-based Pharmaceutical Industry
NSAID	NonSteroidal AntiInflammatory Drug
PAR	Populated Attributable Risk
PHARMO	Pharmaco-Morbidity Linking System
PRISMANT	As per January 1, 2000, NZi and SIG merged into PRISMANT
RIVM	National Institute of Public Health and Environmental Hygiene
SFK	Stichting Farmaceutische Kengetallen
SIG	SIG Care Information, Holder of the LMR Registration
U-Expo	U-Expo Cooperation, Holder of the U-Expo drug data