The role of Health Insurance Companies in optimising drug prescription in Primary Care; the example of acid suppressing drugs

Hugo M. Smeets

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The role of Health Insurance Companies in optimising drug prescription in Primary Care; the example of acid suppressing drugs

De rol van zorgverzekeraars bij het optimaliseren van het voorschrijven van geneesmiddelen in de Eerstelijnszorg; het voorbeeld maagzuurremmers

(met een samenvatting in het Nederlands)

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Contents

1 Introduction

Health Insurance Companies in the Netherlands

In the nineteenth century initiatives for a social insurance for health problems were introduced in the Netherlands, mainly through the labour unions. For a long time the so-called Sick Funds like 'Union is Strength' and 'Help with Health' remained isolated initiatives for special groups of residents.[1] It was only during the German occupation in the Second World War that a formal system of income- dependant social health insurance was introduced. From 1941 onwards anyone with an income below a nationally established limit entered one of the regional Sick Funds.[2] This system proved to be a successful instrument to guarantee access to health care facilities for the majority of the population, especially for the lower income group. The Sick Funds continued functioning for decades but over time their mission changed. Until the nineties, their role was mainly administrative, simply carrying out the health insurance legislation of the government. Politicians determined the size of the national health care budget, and governmental bodies determined which health care facilities were reimbursed and to what extent. This system of fixed reimbursement prices was also leading for the much smaller private insurance sector that functioned parallel to the Sick Funds.

After the nineties the tasks and mission of the Sick Funds changed. In that decade a period of deregulation started. The government retreated from its coordinating and regulating role in the health care sector in an attempt to improve cost-effectiveness.[3, 4] Sick Funds were now supposed to contribute to a more patient oriented, market-directed health care system, and were allowed to recruit policyholders outside their own region to stimulate mutual competition.[5] It turned out to be the overture for the elimination of the Sick Funds. In 2006, the Sick Fund Act was replaced by the new Health Insurance System, which was created to provide every Dutch citizen with a basic health insurance, independent of income.[6] With the introduction of marketing principles in the new health care system the government largely withdrew from detailed regulation of the health care expenditure. Individual insurance compa-

nies, which emerged from the former Sick Funds, acted as business companies in a free market with far less government influence. Their mission was to provide optimal healthcare facilities for their policyholders, in a cost-effective way. Although this mission is comparable to that of Health Maintenance Organisations in the USA, the insurance companies remain 'not for profit' organisations, subject to political influence on the overall health budget. After the introduction of the market principles in the health sector the former Sick Funds initially focussed on preserving as many policyholders as possible through competing on insurance fees. In a later stage they included cost reduction and structured quality of care programmes in their policy.[7] The underlying idea of these plans was that in the long run the investment in improvement of quality of care would lead to a decrease in healthcare costs. In order to achieve this, insurance companies aim for a system of special contracts with healthcare providers in primary, secondary and tertiary care, to guarantee quality of care as well as control of expenditure.[8, 9]

Initiatives to control drug prescription

Through the Sick Fund Act the Dutch government has always played a leading role in the reimbursement of drug prescription. In attempts to control the annually growing drug expenditure the government followed restrictive policies, by for instance excluding drugs from reimbursement or cutting on the increase of the pharmacists' tariffs. Several measures were implemented, such as the introduction of 'the 90 days prescription measure' (maximum refill for 3 months), 're-pricing of drugs' (maximum reimbursement up to the average cost level in surrounding European countries), and 'reduction of pharmacy fees' (less compensation for the services of pharmacists).[10]

As drug prescription remained one of the major expenditures, also after the introduction of the new Health insurance system, control of pharmacotherapy was of vital interest to the insurance companies. Because of the need for budget control and by using the

freedom they were given under the new act, many insurance companies started managed care prescription projects. The aim of these initiatives was usually twofold: to reduce the costs of unnecessary prescriptions and to improve the quality of pharmacotherapeutical care.[11]

One of the most discussed initiatives came from Menzis, a leading insurance company in the Netherlands. Menzis linked a policy of preferred prescription of generic drugs directly to the income of general practitioners (GPs). GPs received a bonus if more than eighty percent of their prescribed proton pump inhibitors (PPIs) and cholesterol lowering agents (statins) were generic. As the generic forms of these drugs are considered equally effective as the patented drugs an important cost saving was foreseen.[12] As expected, the responses from professional and patient organizations were negative; doctors feared this measure would threaten their professional autonomy, while patients, and also some doctors, questioned the non-inferiority of the generic drugs and felt that too many patients were denied necessary drugs. Despite the lawsuits of pharmaceutical companies the Menzis initiative was rapidly accepted, both by patients and professionals, and became a great success in terms of cost reduction.

Rationalising acid-suppressing drug prescriptions

Over the past decades the costs of drug prescriptions, especially those for dyspeptic complaints, have had a major impact on health expenditure across Europe. In 2008, 13% of the Dutch population was using acid-suppressing drugs (ASDs), of which over 90% were PPIs.[13] Approximately one third of these patients use more than 180 Defined Daily Dosage (DDD) annually, and can be considered chronic ASD users.[14] The annual costs for ASDs exceed more than 6% of the national pharmacy budget of 5 billion Euros. Before 2004, the costs for ASD took up even more than 10% of the budget. The expiration of the patent of omeprazol, the most frequently prescribed PPI, made the price drop with 50%. Because of the preferential policy of the insurance companies, with reimbursement of the

cheapest generic variant only, the annual increase in ASD prescriptions temporarily levelled. To date, however, excessive prescription of ASD, especially of PPIs, remains an important problem, and both professional organisations and insurance companies continue their efforts to optimise prescription policy in patients with dyspepsia.

Management of dyspepsia After the discovery of the bacterium *Helicobacter Pylori* in the stomach by BJ Marshal and JR Warren the number of peptic ulcers decreased dramatically. In contrast, the use of acid-suppressing drugs continued to increase every year.[15, 16, 17, 18] Eradication of *H. Pylori* is considered the single effective treatment for patients with peptic ulcer, but in daily practice many patients continue on a maintenance regime of ASD after eradication therapy. Even more important is the wide spread prescription of PPIs in patients with (non ulcer) dyspepsia and reflux symptoms, often on a day-to-day basis.[3, 19, 20, 21, 22, 23, 24] It is suggested that due to the high effectiveness of ASDs for acid related symptoms, the high placebo effect and the absence of side effects, professionals take a pragmatic approach towards prescription, thus creating unnecessary drug dependency.[25, 26, 27] Although other factors such as the increased use of NSAIDs and the increased prevalence of overweight and psychological problems are thought to contribute to the increase in ASD prescription, there is no evidence-based indication for daily ASD consumption in most of the patients using it.[28, 29, 30, 31, 32, 33, 34, 35] In national and international dyspepsia guidelines continuous use of ASD is only recommended in case of persistent reflux symptoms or severe oesophagitis grade C and D.[36, 37] Based on epidemiological data less than 40% of the patients with reflux symptoms have oesofagitis, of whom only 10% have severe inflammation or strictures.[38, 39, 40] Most patients with persisting reflux symptoms are not referred for endoscopy. For these patients guidelines recommend empirical ASD therapy for 4-8 weeks. As the majority of patients with reflux complaints are managed in primary care, most of the annual increase in ASD prescription is considered to originate from prescription by general practitioners.[41, 42, 43]

Initiatives to optimise ASD prescription

Professionals In 1993, the first professional guideline for the management of dyspepsia was published by the Dutch Scientific Association of General Practice (NHG). The guideline was updated in 1996 and 2003.[36] Because of the need for a consistent inter-professional approach in the management of dyspepsia a multidisciplinary working group under guidance of The Dutch Institute for Healthcare Improvement (CBO) published a multidisciplinary guideline for management of dyspepsia in primary and secondary care.[44] Both the primary care and the multidisciplinary guideline were published in widely read Dutch professional journals and were presented at scientific conferences. To further stimulate adherence with the guidelines, implementation packages including patient information leaflets were distributed among regional professionals. These packages were also used during postgraduate training sessions, and in vocational training programmes in general practice. Most GPs in the Netherlands routinely participate in pharmacotherapy control programmes and patients are usually willing to cooperate in programmes aimed at optimising drug therapy.[45] Some studies have indeed demonstrated the successfulness of patient-directed intervention strategies in order to achieve drug treatment targets recommended in clinical guidelines.[46, 47] Despite the introduction of dyspepsia guidelines and the presumed cooperation of patients, professional initiatives to rationalise ASD prescription so far have not been very successful.[14]

Government Traditionally the government itself does not control the quality of pharmacotherapy; this is left to professional organisations or independent regulatory bodies. Because of the major impact on the health budget an exception was made for proton pump inhibitors and statins. The government intended to label ASD as a so-called "life style" drug; the indication for these drugs was considered to result from an unhealthy lifestyle. Given this "individual responsibility", for in this case dyspeptic symptoms, ASDs were excluded from financial compensation.[49]

This proposal met so much opposition from both professionals as well as patients that actual implementation was considered unwise.

Health insurance companies Because promotion of quality of care is part of their mission, many Health Insurance Companies introduce managed care projects to improve the costs-effectiveness of pharmacotherapy. Studies demonstrate, however, that implementation strategies that were evaluated in these managed care projects are often not successful. It appears to be difficult for professionals to adapt their prescription policy without supportive intensified interventions.[50] Strategies with simple protocol instructions or other passive recommendations exert only minimal or no effects.[51, 52] For example, strategies aimed at involving professionals more actively in the overall care process of patients with dyspepsia did not reduce ASD prescription rates.[53] In contrast, a small-scale ASD reduction strategy among GPs with multiple active interventions did provide beneficial effects.[46] For effective implementation of ASD prescription guidelines Health Insurance Companies need to develop managed care projects with multiple active strategies on a much larger scale, which focus on the prescribing professional as well as on the patient. One of the most effective strategies is probably to encourage GPs and patients to convert chronic day-to-day use of ASD into a symptom guided on-demand regimen.[54, 55] Under this regime patients only take ASD in case of actual reflux symptoms. Currently the on-demand therapeutic regimen is insufficiently practiced, but it offers a good opportunity for ASD control programmes from insurance companies.[56]

Aim of the studies presented in the thesis: Evaluation of a Health Insurance Company induced ASD reduction strategy

Agis, one of the major insurance companies in the central region of the Netherlands, launched a managed care project to reduce chronic ASD prescription. For optimal implementation of this project Agis used multiple strategies. All the GPs in the Agis region were invited

to participate and received a protocol to guide them in rationalising ASD prescription in clinical practice. They received an overview of patients in their practice presently taking ASD chronically and information material to motivate these patients to reduce ASD consumption. Agis applied different strategies to support the participating GPs; telephone support and practice visits by specially trained nurses.[57, 58, 59] To ensure optimal cooperation GPs were offered extra consultation fees as compensation for the time invested.[60]

In the studies presented in this thesis we explore the potential role of the Health Insurance Company in rationalising the drug prescription policies of medical professionals, by evaluating and analysing this Agis managed care ASD programme. Our specific objective was to evaluate the effectiveness of active and passive strategies for implementation of a Health Insurance Company initiated managed care programme in reducing the prescription of antacid drugs in primary care practice. Secondary objectives were to evaluate epidemiological trends in the prescription of ASD, either as antacid treatment or as gastro protective agent in patients using NSAIDs, to asses the willingness of GPs and patients to participate in insurance company initiated ASD reduction programmes, and to evaluate the potential and reliability of the insurance company database for scientific research.

Outline of this thesis

In the first chapters we illustrate the extent of the problem by analysing trends and determinants of ASD prescription in the Netherlands. In chapter 2 we report the prevalence of ASD use in three consecutive years, based on data extracted from the Agis Health Database. In addition, we analysed patients and GPs' determinants of ASD prescription. As part of this increase in ASD prescription may be explained by the growing need for gastroprotective medication in patients using NSAIDs we separately report trends, determinants and adequacy of gastric protective PPI prescription in patients using NSAIDs in the Agis region (chapter 3).

In chapter 4 the results of a systematic literature review on the efficiency of implementation strategies for rationalising ASD prescription are reported. Based on this literature review Agis launched a managed care project for reduction of ASD prescription in its own region. In chapter 5 we describe the outline of this managed care project and the results of its implementation in a pilot study in the Amsterdam region. For an optimal implementation of a prescription rationalisation programme acceptance and cooperation of patients is essential. Therefore we explored the patients' view on the potential role of the insurance company in changing prescription policies in a survey among a representative patient sample in the Agis region (chapter 6).

In chapters 7 and 8 the results of a randomised controlled trial to evaluate different strategies that were used for implementation of the ASD reduction project are reported. In chapter 7, the effectiveness of a passive implementation strategy and in chapter 8 the effectiveness of two different active strategies are presented. The studies reported in chapter 2, 3, 5, 7 and 8 were all performed with data from the insurance company. In chapter 9 we analyse the reliability of this Agis Health Database and explore the potential value of databases of health insurance companies for clinical research.

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Trends and Determinants of Pharmacotherapy for Dyspepsia: Analysis of 3-Year Prescription Data in The Netherlands

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2 Trends and determinants of Pharmacotherapy for dyspepsia: analysis of 3-year prescription data in the Netherlands

Introduction

Consumption of acid-suppressing medication, i.e. proton- pump inhibitors (PPI), has increased greatly over the past decade. Healthcare expenditure on antidyspeptic medication comprises more then 10% of the total annual budget of several Western countries. In the past 5 years the volume of acid-suppressing medication has increased by 50% in The Netherlands.[1] Since only part of this increase can be explained by an increasing incidence of the disease, questions arise as to the determinants of use of this medication. We aimed to identify trends in use of antidyspeptic medication in order to determine patient-related and physician-related variables related to these trends, and to determine the influence of endoscopy on this use.

Methods and Results

We analysed the 3-year registration data of the prescriptions and diagnostic procedures of a regional Health Insurance Company (ANOVA) in The Netherlands, where 60%–70% of the population have compulsory health insurance. All Dutch GPs and specialists collaborate with these companies. Health service consumption is registered at individual level in a detailed standardized format. Apart from descriptive and bivariate analysis, multivariable analysis (ANOVA) correcting for GP age, urbanization, practice organization, referrals and list size was used to identify GP-related predictors of prescription rates. The analysis comprises over 70,000 users and 580 GPs. Eighty-five percent of the volume is prescribed by GPs. There is a 6%–10% annual increase of total volume used and there is an increase of chronic users: in 1999, 44% of PPI users used more than 180 DDD/year. The fastest growing group comprises elderly women, who already consume over a quarter of the total volume. Concomitant use of NSAIDs (40%) and laxatives (22%) is common. A first endoscopy was registered in 8788 (12%) of users. Thirteen percent initiated antidyspeptic medication (mainly PPI), whereas 20% terminated use after endoscopy. In multivariable analysis we found that the number of endoscopies requested (standardized coefficient

0.32, $p = 0.000$) and overall prescription rate (standardized coefficient 0.13, $p = 0.000$) remained significantly associated with PPI prescription rates. This model predicts 12% of prescribing behaviour variance.

TABLE 1 **Predictors of standardized prescription of antidyspeptic drugs; results of multivariable analysis**

Variable	Beta	Significance
No. of endoscopies	0.32	0.000
No. of prescriptions/patient/year	0.13	0.000
GP age group	-0.47	0.37
Urbanization	-0.011	0.85
Practice organization	0.048	0.36
Referrals to any specialist	0.072	0.38
List size	-0.009	0.90

Percentage predicted variance: 0.12

Comment

Consumption of antidyspeptic medication is increasing in patient groups that are probably most at risk of serious complications; endoscopy has a decisive role in prescription; there appears to be a group of more 'intervention-prone' GPs with higher PPI prescription rates. Several limitations may impair the validity of our study: ANOVA serves mainly sick fund patients, and only few privately insured patients who may have different healthconsumption patterns. Relevant GP characteristics (vocational training involvement, specialization, CME activities) are not included in the database. However, similar trends in the development of antidyspeptic medication have been described for the UK.[2] Jones et al. suggest that GPs generally follow the example of teaching hospitals.[3] Age, longevity, co-morbidity and co-medication render elderly women more liable for development of peptic ulcer disease providing an explanation for the observed trend. The shift towards PPI use after endoscopy is important. Endoscopists usually give medication

advice after endoscopy; open access endoscopy services report
4 abnormal findings in no more than 45% of endoscoped patients. ←
Even with a considerable proportion of endoscopy-negative reflux disease (responding best to PPI treatment), the post-endoscopy shift towards PPI is largely irrational. On the other hand, endoscopy leads
5 to termination of medication use, confirming earlier studies.← We conclude that the increase in antidyspeptic medication consumption mainly reflects elderly women; it is correlated to NSAID use and can only to a minor extent be explained by prescriber differences.

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Trends and determinants of adequate gastroprotection in patients chronically using NSAIDs

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3 Trends and determinants of adequate gastroprotection in patients chronically using NSAIDs

Abstract

Purpose To identify determinants and trends of gastroprotection in patients chronically using NSAIDs.

Methods design retrospective cohort study. Data source: Agis Health Database (AHD) containing annual prescription records of approximately 1.5 million patients. Patients: All patients using more than 180 Defined Daily Doses (DDD) annually, of any NSAID from 2001 to 2007. Main outcome measures: prevalence of NSAID use, adequate prescription of gastroprotective drugs (PPI, misoprostol or COX-2 inhibitor use), determinants of adequate gastroprotection.

Results The percentage of patients chronically using NSAIDs rose from 7.3% of the total NSAIDs users in 2001 to 7.5% in 2007. The percentage of patients on NSAIDs receiving adequate gastroprotective medication in line with actual guidelines increased from 39.6% in 2001 to 69.9% in 2007. Age over 70, co-prescription of SSRI, coumarine and steroids and arthritis are the main clinical factors predicting adequate prescription.

Conclusions The prevalence of NSAID prescription and the risk of gastric complications is increasing steadily. Although the number of patients receiving gastroprotective medication is also increasing, over 30% of the patients at risk for GI complications are left unprotected in 2007. In order to improve protection rates in patients using NSAIDs and to decrease NSAID related hospital admissions in the future, the implementation of gastroprotection guidelines needs to be improved.

Introduction

Non Steroidal Anti Inflammatory Drugs (NSAIDs) are frequently used world wide. In the Netherlands in recent years around three million patients (18.5% of the Dutch population) were prescribed NSAIDs, corresponding with over 5% of all prescriptions.[1]

The use of NSAIDs is associated with various adverse effects. Gastrointestinal complications, ranging from mild dyspepsia to serious complications such as bleeding and perforation, occur frequently. Mild dyspepsia is seen in 35% of patients using NSAIDs, peptic ulcer occurs in 14-31% and severe complications, such as bleeding or perforation, are reported in 1-4%.[2, 3]

In Spain, one third of the preventable adverse drug events leading to hospital admission are related to the use of NSAIDs or aspirin.[4] In the UK the annual number of emergency admissions associated with the use of NSAIDs is about 12,000, leading to 2,500 deaths.[5, 6, 7] In the Netherlands 2.800 NSAID related hospital admissions were reported in the year 2000, causing 165 deaths.[8]

Gastroprotection is advocated for patients using NSAIDs in high risk groups to prevent gastric complications. There is ongoing debate about the indicated risk groups and the optimal gastroprotective agents.

Several international guidelines have provided guidance on gastric protection in patients using NSAIDs, and described risk groups and recommendations for gastroprotective drugs.[9, 10, 11] In these guidelines a history of peptic ulcer disease and increasing age are generally accepted risk factors. In the Netherlands the multidisciplinary evidence based practice guideline 'NSAID use and the prevention of gastric damage' published by the Dutch Institute for Health Care Improvement (CBO) describes the risk groups and indications for gastroprotection in patients chronically using NSAIDs, and indicates different levels of urgency for gastroprotection. For patients chronically using NSAIDs with a history of peptic ulcer or *H. Pylori* infection, and for those over the age of 70, gastroprotective medication is *mandatory*. In patients between 60 and 70 or in case other risk factors[table 1] are present, gastroprotection should be *considered*.

TABLE 1 **Risk factors for gastric complications in NSAID users and indications for gastroprotection as mentioned in different European multidisciplinary clinical practice guidelines**

NICE guideline for dyspepsia ↓	SIGN guideline for control of Pain in Patients with Cancer ↓	CBO guideline 'nsaid use and the prevention of gastric damage' ↓
Risk factors		
History of peptic ulcer (PUD)	Age over 60 years Smoking History of peptic ulcer (PUD) Concomitant use of an NSAID and: - oral steroids - anticoagulants Co-morbidity: - renal disease - heart failure - hepatic impairment	*Absolute risk factors* (gastroprotection mandatory): Age over 70 years History of peptic ulcer (PUD) *H. Pylori* infection *Relative risk factors* (gastroprotection to be considered): 60 to 70 years of age Concomitant use of an NSAID and: - coumarine or salicylic acid derivatives - corticosteroids - selective serotonin re-uptake inhibitors Co-morbidity: - Diabetes - Heart failure -Severe rheumatoid arthritis High-dose / long term NSAID use Multiple NSAID use
Recommended type of gastroprotection		
misoprostol proton pump inhibitor double dose H2R	misoprostol proton pump inhibitor substitution of a "classic NSAID" by a cyclo-oxygenase -2-selective NSAID. ↓	misoprostol proton pump inhibitor substitution of a "classic NSAID" by a cyclo-oxygenase-2-selective NSAID
10	*11* *11, 24*	*9*

9, 10, 11 The recommendations are generally in line with other Western European guidelines. ←

All guidelines recommend proton pump inhibitor or misoprostol as adequate gastroprotective agents, and most guidelines consider the use of single or double dose of H2 blocking agents as inadequate. The substitution of a classical NSAID by a COX-2 inhibitor was

supposed to be an effective alternative, though recently the place of these agents has become subject of discussion given their cardiovascular side effects.
Studies performed in the Netherlands on prevention of gastro-intestinal complications before implementation of the Dutch guideline in 2004, demonstrated low rates of adequate gastroprotection among NSAID users. In these studies only 13 to 23% of NSAID users with a risk factor for gastro-intestinal complications received a gastroprotective agent.[12, 13]

Given the high prevalence, the considerable morbidity and mortality and the large economic impact of gastrointestinal complications in NSAID use, the implementation of these guidelines in daily clinical practice is essential. We analysed trends in prescription patterns of NSAIDs and gastroprotective drugs and report adherence to the Dutch guideline on gastroprotection in NSAID use from the year 2001 to 2007.

Methods

Design A retrospective cohort study was performed in the Health Database of Agis, a major insurance company in the Netherlands. The Agis Health Database (AHD) contains the demographic and health care consumption data of approximately 1.5 million inhabitants. As all prescriptions must be registered electronically in this database before costs are reimbursed, the AHD is an accurate registration of all pharmacotherapeutical prescriptions of GPs and specialists.

Cases Patients chronically using NSAIDs (defined as patients using more than 180 Defined Daily Doses of any NSAID annually) in the period 2001 to 2007 were identified. Per year for each selected patient the presence of risk factors for gastric side-effects as well as the co-prescription of gastroprotective medication (proton pump inhibitor, misoprostol, or use of a COX-2 inhibitor of more than 180 DDD annually) was assessed.

Risk factors We analysed data in the perspective of the risk factors and indications for gastroprotection as described in the Dutch clinical guideline 'NSAID use and the prevention of gastric damage.' ← *table 1; 9*

As the AHD contains quantitative information on health care consumption data only, and not qualitative data (such as clinical diagnoses), several proxy indicators were used to identify disease specific risk factors. Most of these proxy indicators are drugs that are prescribed in relation to the risk factor under study. ← *table 2* They were extracted from the Dutch clinical practice guidelines. In the AHD,

TABLE 2

Risk factors as mentioned in the Dutch multidisciplinary guideline and the proxy indicators for these risk factors used in this study (description, ATC code)

Risk factors	Description and ATC code
Age	Age on July 1st in the year of prescription
History of peptic ulcer / *H.Pylori* infection	Triple therapy in year of prescription or the combination of a Proton pump inhibitor, Amoxicillin and Claritromycin at the same time ATC codes: A02BD or the combination of A02BC, J01CA04, and J01FA09
Coumarine or salicylic acid derivative use	ATC code: B01A
Corticosteroid use	ATC code: H02
Selective Serotonin Re-uptake Inhibitor use	ATC code: N06AB
Diabetes	Diabetes medication : ATC code A10
Heart failure	Diuretic combined with an ACE inhibitor, an AII-antagonist or digoxin ATC codes: C03 combined with C09A or C09B or C09C or C09D or C01AA05
Severe rheumatoid arthritis	Disease modifying anti-rheumatic drugs ATC codes M01CB, M01CC, L04AA, L04AX, P01BA01, P01BA02)
High-dose NSAID use	more than 360 DDD of any NSAID annually
Multiple NSAID use	more than one type of NSAID used annually

these drugs are labelled with ATC codes ('Anatomical Therapeutic Chemical Classification System'). ← *14; table 2*

Outcomes The primary outcome parameter was the annual percentage of patients chronically using NSAIDs that was correctly receiving gastroprotection, according to the Dutch guideline.

Analysis For each patient we analysed the number of risk factors for which gastroprotection is *mandatory* according to the guideline, and the number of risk factors for which gastroprotection should be *considered*. We compared these theoretical indications to the actual prescription of gastroprotective medication in these patients.

Adequate gastroprotection was defined as (1) chronic NSAID use (except COX-2 inhibitor) in the presence of one or more risk factors for GI complications, with co-prescription of more than 180 DDD of a proton pump inhibitor or misoprostol in the same year, or (2) the use over 180 DDD of a COX-2 inhibitor. Double gastroprotection was defined as 'the chronic use of two or more gastroprotective agents in the same year', for instance the combined use of over 180 DDD of both a cox-2 inhibitor and a PPI or a PPI and misoprostol.

To evaluate the compliance with the CBO guideline we made cross tabulations for gastroprotection and the risk factors for which gastroprotection was mandatory or for which it should be considered. ← *table 3* To determine the impact of individual risk factors on the prescription of gastroprotection, we performed univariate and multivariate logistic regression, the results of which were reported in adjusted OR. ← *table 4*

Results

Prevalence of NSAID prescription In the time period 2001-2007 the average number of patients using an NSAID in the Agis Health Database was 207,910 annually. Time trend analysis demonstrates that the annual population

TABLE 3 **Annual rate of adequate gastroprotection (GaP) rate according to the recommendations in the Dutch multidisciplinary guideline; percentage of all patients chronically using NSAIDs in the period 2001-2007**

Year	"GaP mandatory and adequately prescribed"		"GaP to be considered and adequately prescribed"		"GaP not mandatory and not to be considered but prescribed"	
	N	%	N	%	N	%
2001	1986	39.6	2429	30.5	870	24.4
2002	2897	48.5	3482	37.3	1278	33.0
2003	3659	56.4	4522	45.3	1833	43.1
2004	4711	63.3	6569	51.5	2553	46.0
2005	3673	61.4	5365	48.2	1812	41.9
2006	3491	65.5	4854	50.7	1484	41.7
2007	3517	69.9	5332	56.7	1481	44.5

TABLE 4 **Determinants of adequate gastroprotection in patients chronically using NSAIDs in 2007**

Risk Factors	Univariate Odds ratio	95% CI **		Multivariate* Odds ratio	95% CI **	
Age 70+	2.0	1.9	2.2	2.0	1.8	2.1
Age 60-70	1.1	1.0	1.2	1.4	1.3	1.5
Multiple NSAID use	0.9	0.7	1.3	1.3	0.9	1.8
High dose NSAID use	0.7	0.6	0.7	0.7	0.6	0.7
Ulcus pepticum or *H.Pylori* in history	0.5	0.3	0.9	0.4	0.2	0.8
Coumarine and salicylic acid derivatives	2.0	1.8	2.1	1.5	1.4	1.7
Corticosteroid use	1.8	1.7	2.0	1.6	1.5	1.8
SSRI use	1.5	1.4	1.7	1.7	1.6	1.9
Diabetes	1.3	1.2	1.4	1.1	1.0	1.2
Heart failure	1.7	1.6	1.8	1.3	1.2	1.4
Arthritis	1.5	1.4	1.7	1.7	1.5	1.8
Constant	-	-	-	0.9	-	-

* The multivariate model included all risk factors from the univariate analyses with p>0.10
** 95% CI = 95% confidence interval

prevalence of NSAID use increased from 14.3% in 2001 to 19.1% in 2007. The percentage of patients chronically using NSAIDs rose from 7.3% of the total NSAIDs users in 2001 to 7.5% in 2007. Of all 17,763 patients chronically using NSAIDs in 2007, 11,041 (62.2%) used more than 270 DDDs annually. The mean age of the chronic NSAID users was 59.1 in 2001 and 59.9 in 2007 (diff 0.8, 95% CI 0.3 – 1.2).

Risk factors for gastric complications In 2007, 81.3% (N=14,433) of the patients chronically using NSAIDs had one or more risk factors for gastric complications. Of these, 35.0% (N=5035) had at least one risk factor for which gastroprotection was *mandatory* according to the Dutch guideline and 65.0% (N= 9,398) had at least one risk factor for which gastroprotection should be *considered* (but not mandatory).

NSAID use and Gastroprotection In 2007, 69.9% (N=3,517) of the patients chronically using NSAIDs with at least one risk factor for which gastroprotection was *mandatory*, was adequately protected. Additionally 56.7% (N=5,332) of the patients with at least one risk factor for which gastroprotection was to be *considered* were prescribed a gastroprotective agent in line with the recommendations of the guideline.← In total 9.1% (N=1,623) of the patients on chronic NSAIDs received double gastroprotection.

table 3

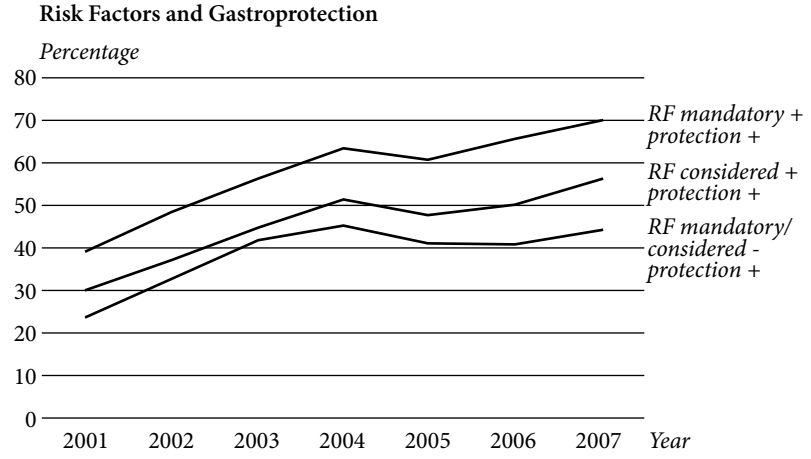
Time trend analyses demonstrate that for those patients chronically using NSAIDs with a risk factor for which gastroprotection is mandatory, the prevalence of gastroprotection increased from 39.6% (N=1,986) of the indicated population in 2001 to 69.9% (N=3,517) in 2007.← Through the years the gastroprotection rate in patients with a risk profile for which gastroprotection should be considered rose equally.← Double protection in patients chronically using NSAIDs increased from 3.9% (N=643) in 2001 to 9.1% (N=1,623) in 2007 (not in table).

table 3

figure 1

FIGURE 1

Annual rate of adequate gastroprotection (%) according to the Dutch multidisciplinary guideline; time trend 2001-2007



Univariate analyses demonstrated several determinants associated with adequate prescription of gastroprotection. ← *table 4* After adjustment in multivariate analysis age above 70 had the strongest association with adequate gastroprotection (OR 2.0), followed by SSRI use (OR 1.7), arthritis (OR 1.7), corticosteroids (OR 1.6) and coumarines (OR 1.5). Multiple NSAID use and DM was not associated, while high dose of NSAID and *H. Pylori* history had a negative association with adequate gastroprotection. ← *table 4*

Discussion

Although the percentage of patients who received adequate gastroprotection has steadily risen to almost 70% over the past 7 years, over 30% of the patients at risk for serious gastro-intestinal side effects because of chronic NSAID use are still left unprotected. If these patients were provided with adequate gastroprotection, a substantial decrease in NSAID related hospital admissions and deaths are to be expected. Van Soest et al. demonstrated a four-fold increased risk of upper gastro-intestinal complications for patients using NSAIDs in case of non-adherence to gastroprotective drugs. ← *15* The benefits of a decrease in illness and costs would amply surpass

the extra costs involved in providing extra gastroprotective pre-
16 scriptions.←

There is ongoing debate about the contribution of individual risk
17 factors to the prescription of gastroprotective medication.← In this large cohort we could confirm an independent contribution for most of the risk factors mentioned in the literature, with the exception of Diabetes and the use of multiple NSAIDs. High NSAID dose and a history of peptic ulcer, as identified by *H. Pylori* treatment, had a negative association with the prescription of adequate gastroprotection. The latter might be explained by the fact that after successful peptic ulcer treatment by *H. Pylori* eradication physicians tend to omit additional gastroprotection in case of NSAID use in future.

The time trend analysis demonstrates a steady increase in gastroprotection rate in the Agis database from 2001 to 2007 in adequate, as well as in double protection. We observed a temporary levelling of this time trend in 2005. This was probably caused by the decrease in the use of COX-2 inhibitors prescriptions, due to the reported cardiovascular side-effects. A similar phenomenon was reported for the 2001-2007 gastroprotection rates in the US.18 which was generally considered to originate from the negative publicity concerning COX-2 inhibitors. Notably, the decrease in the use of COX-2 inhibitors was not compensated by additional gastroprotective therapy
18 with PPI or misoprostol.←

The Dutch clinical guideline 'NSAID use and the prevention of gastric damage' was published in March 2004. We could not demonstrate a direct positive effect of implementation of the guideline on gastroprotection rates. Even though the cox-2 publicity may have negatively influenced the prescription of gastroprotective drugs, it is obvious that the implementation of the guideline 'NSAID use and the prevention of gastric damage' among clinicians needs improvement. Recent studies on guideline implementation

concluded that an active approach, using an implementation protocol and focussing on potential barriers results in better adherence to the recommendations of the guideline.[19, 20]

In the design and analyses we made a number of choices that may have had impact on the results. We defined chronic use of NSAIDs and gastroprotective agents as the prescription of more than 180 DDD annually. This is only a proxy definition and not an absolute reflection of day-to-day-NSAID use. In theory a small proportion of patients could have used both NSAID and PPI sequentially, resulting in an overestimation of the percentages of gastroprotection. However, knowing that in daily practice most patients use NSAIDs on an intermittent or on demand basis, and that sequential use of PPI and NSAIDs for a 6 months period is exceptional, we think that this definition adequately reflects the population at risk.
We did realise that PPIs are mainly used for treatment of dyspeptic complaints, but we could not discriminate curative from preventive indications. In addition, by using the *H. Pylori* treatment as proxy indicator we missed the *H. Pylori* negative peptic ulcers. This implies that our data might slightly overestimate the adequacy of gastroprotection, as part of the PPI prescription in patients using NSAIDs is not preventive but actually treatment of dyspeptic side effects, and the small number of these *H. Pylori* negative ulcers are not included.

There is ongoing debate about the effectiveness of H2 receptor antagonists, which would only be gastroprotective in double dose. The predominant opinion is that H2 receptor antagonists are not first choice to protect against the severe gastrointestinal complications of NSAID use such as bleeding and perforation.[21, 22, 23, 24] Therefore we decided not to consider H2 receptor antagonists as adequate gastroprotective agents.
We had to use proxy indicators for the assessment of risk factors, as the Agis Health Database does not contain qualitative information about most of these clinical risk factors. Although the use of proxy

definitions based on ATC codes may have affected the accuracy of the analysis, we think that, given the limitations of the database, this was the best option.

The Agis database does not provide information about 'over the counter' medication. Although PPI and misoprostol are not available over the counter, NSAIDs are. In addition we could only monitor prescription, and not the actual use of gastroprotective medication. This may have resulted in an underestimation of the chronic use of NSAIDs and an overestimation of the adequate protection rate in our calculations. Enquiries about the use of NSAIDs bought 'over the counter' should be routine in clinical practice of GP's and specialists.

We think that due to the size and the representativeness of the Agis Health Database, its reliable verification measures, and the fact that it provides information on the prescriptions of both specialists and general practitioners, the results of our study are a valid and reliable reflection of the time trends in gastroprotection in the Netherlands. Even though our study had some methodological limitations, the fact that we could study all risk factors that were included in the multidisciplinary guideline adds value to the conclusions.

Conclusions

Although the number of patients with adequate gastroprotection has risen steadily in recent years, in 2007 still over 30% of the patients at risk are left unprotected. Our study did not analyse the reasons why over 30% of patients did not receive gastroprotection. Future qualitative research should determine whether physicians consciously omit gastroprotection in individual patients after careful evaluation or if other reasons (unawareness of NSAID use, lack of knowledge about gastroprotective measures and indications) do play a role. In order to improve protection rates in patients using NSAIDs and to decrease NSAID related hospital admissions in the future, the implementation of guidelines on gastroprotection among physicians needs to be improved.

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Effectiveness and costs of implementation strategies to reduce acid suppressive drug prescriptions: a systematic review

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4 Effectiveness and costs of implementation strategies to reduce acid suppressive drug prescriptions: a systematic review

Abstract

Background Evaluation of evidence for the effectiveness of implementation strategies aimed at reduces prescriptions for the use of acid suppressive drugs (ASD).

Methods A systematic review of intervention studies with a design according to research quality criteria and outcomes related to the effect of reduction of ASD medication retrieved from Medline, Embase and the Cochrane Library. Outcome measures were the strategy of intervention, quality of methodology and results of treatment to differences of ASD prescriptions and costs.

Results The intervention varied from a single passive method to multiple active interactions with GPs. Reports of study quality had shortcomings on subjects of data-analysis. Not always all outcomes were calculated but if so reduction of prescriptions varied from 8% up to 40% and the cost effectiveness was in some negative and others positive. Few studies demonstrated good effects of the interventions to reduce ASD.

Conclusion Poor quality of some studies is limiting the evidence for effective interventions. Also it is difficult to compare cost-effectiveness between studies. However, RCT studies demonstrate that active interventions are required to reduce ASD volume. Larger multi-intervention studies are necessary to evaluate the most successful intervention instruments.

Introduction

Analysis of the use of dyspeptic medication demonstrate that acid-suppressive drugs (ASD) are prescribed in 10% of the population each year.[1, 2, 3] Three percent of these patients are chronic users (>180 DDD), mostly of Proton-Pump Inhibitors (PPI), of which prescriptions increase 5% every year.[4, 5] Together dyspeptic patients account for almost 11% of the pharmaceutical budget of the public insurance companies in the Netherlands. The Dutch multi-disciplinary guideline on 'Dyspepsia management' recommends PPI therapy for typical reflux symptoms for a maximum of eight weeks.[6] Only severe oesophagitis grade C/D requires long-term treatment with PPI. In most other cases gradual termination is possible. However, many physicians repeat prescriptions without systematic evaluation of symptoms. Consequently Dutch national prevalence data of oesophagitis do not match with the rate of people using ASD, indicating that prescription recommendations are not adequately implemented.[7, 8, 9]

Many patients with recurrent dyspeptic or reflux complaints also believe they have to use ASD lifelong.[9, 10, 11, 12, 13] Rebound effects and not explicit placebo-effects are additional factors for patients' pressure for medication. This calls for GP assisting interventions, aiming at cessation of chronic ASD use.[14, 15, 16] While ASD users consume an increasing part of the pharmaceutical budget, more effective use of resources of health care is necessary.[17, 18] Better affordable strategies to reduce ASD are required to stimulate a rational pharmacotherapy. Traditional strategies of implementation of guidelines, like passive education or economic measurements to optimise particular prescribing management have proven to be ineffective.[19, 20, 21] Grol et al demonstrated that GPs need several attributes to comply with recommendations in guidelines.[22, 23, 24] Suggesting that interventions based on multiple strategies will be more successful when actively implemented. Earlier reviews of dyspepsia guidelines enclosed only studies with single intervention strategies of various backgrounds. Recent reviews also evaluated combined strategies like audit, feedback or outreach visits, but the information provided did not

permit conclusions pertaining the effect on prescription management only.[25, 26, 27, 28] In this review we systematically evaluate the effectiveness of intervention methods for implementation of dyspepsia guidelines with the objective to reduce the volume and costs of ASD prescriptions.

Methods

We performed a systematic literature search from 1995 to 2004 in Medline, Embase and the Cochrane Library which included search parameters of the following subject heading terms: 'dyspepsia', 'guideline', 'medication', 'implementation' and 'costs effectiveness'. Furthermore reference sections in original papers and reviews were screened to find studies otherwise published.

Selection of studies was done in two stages. In the first stage studies were screened by titles and abstracts for the description of involvement in an intervention aimed at changing management of dyspepsia. In the second stage the full text of the selected articles was retrieved to proceed the final selection by two criteria. The first inclusion criterion was that studies met criteria for adequate methodology and design. RCT and cohort follow up studies demonstrating quality criteria of evidence (A, B) set by Jailwala et al, were considered eligible to be included in the review.[29] The second inclusion criterion was the presence of outcome measurements related to reduction of medication: proportion of patients that stopped; the number of prescriptions or mean dosage of ASD; effectiveness of diagnostic tests on prescriptions; prescription costs or total disease related costs. Finally we classified the differences in strategy by which guidelines were implemented in daily clinical care: passive hand-over of (education) materials (I), or active strategies by a single (II) or multiple (III) interaction with patients and/or practitioners.

The criteria selection for design and outcome assessment in the second stage was performed independently by a second reviewer (NdeW) and disagreement was resolved by consensus. Non-systematic studies that did not evaluate the intervention or did not report

outcome measurements were excluded. After a description of the type of intervention of the included studies, from each study the data pertaining to the effectiveness of the intervention were extracted. Outcome figures of prescriptions volume and costs, as well as the expenditures per patient were analysed to compare the differences in effects related to the intervention method.

Results

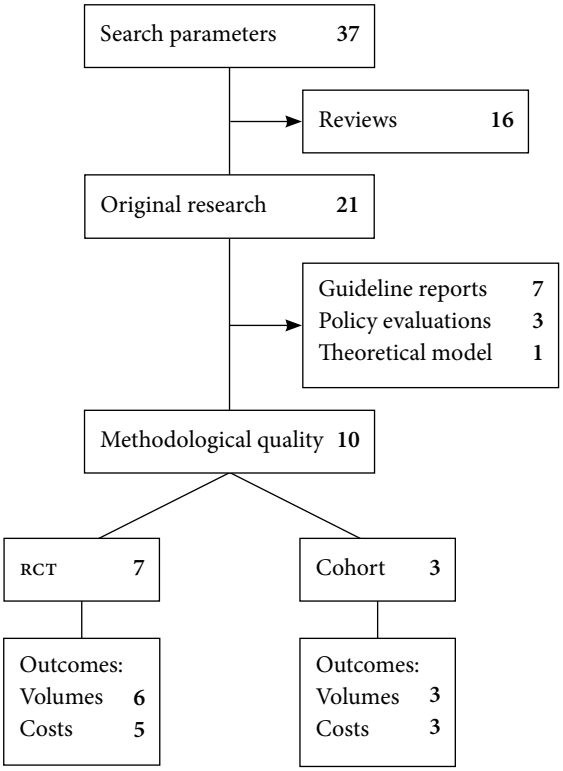
We found 37 articles that met the inclusion criteria, 26 in the search selection and 8 in the reference sections of studies. Of these articles, 16 were marked as review articles and 21 represented original research reports.←

figure 1

Seven of the original studies were excluded because they described guidelines or measured the compliance to guidelines without

FIGURE 1

Eligible studies assessed in review



30, 31, 32, 33, 34, 35, 36 reporting relevant outcomes.← Another three studies were excluded because they were limited to policy evaluations and one study was *37, 38, 39, 40* excluded because it described a theoretical model.←

table 1; 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 Finally, 10 studies were eligible to be included in analysis.← Seven of *43, 44, 45, 46, 47, 48, 50* these studies were designed as RCT (A2).← The inclusion of the research population and baseline similarity for the intervention was well described and five of them included intention to treat analysis, but most studies had shortcomings in reporting outcomes and statistics.

In the cohort studies (B) the number of involved GPs was unknown and outcomes were not reported sequentially and in the multi-centre study (B) was the randomisation procedure unclear.← None of *41, 42, 49* the B qualified studies described physicians' involvement in therapy management and one of them was a direct intervention from the government.← *41*

Three of the 10 selected studies did not evaluate cost-effectiveness. One study focused merely on costs. Excluding the evaluation of governments' intervention on population level (unknown numbers of GPs and patients), the studies involved a total of 847 GPs and/or 3512 patients.

Intervention methods

Intervention methods used in these studies were classified according to three predefined strategies. The first category focused on passive intervention without further implementation activities on individual patient or doctors level and enclosed the two cohort studies (I). The first evaluated the follow up of governmental directives.← *41* The second followed up the revised GP therapy after discontinuing hospital treatment.← *49*

The RCTs were included in the two categories of active single (II) and active multiple (III) interventions. In the first category two studies reported effects of guidelines introduced to the physicians by education and consensus meetings and one study reported effects of a guideline addressed to patients to reduce themselves medication.← *47, 48, 50* In the multiple active category most RCTs reported

about GPs who were educated about guidelines together with active support, feedback or peer visitations during the intervention.[42, 43, 44, 45, 46] The selection process of practitioners and adherence to the intervention were not clearly reported in all RCT studies. The duration of the intervention period as well as the compliance in the groups was not always described systematically. In general RCTs, reported detailed about the intervention strategy.

Effect on the number of Prescription and Diagnostic tests The study on the authorisation program of de government caused a decrease of 80% of all PPI prescriptions.[41] The study in which was addressed to patients to reduce their medication use, ASD prescriptions decreased by 17%.[50] In the remaining eight GP centred intervention studies, half of them introduced and promoted *H. Pylori* tests, while the other half focused on guideline education with feedback strategies, the effects demonstrated variable outcomes. In the *H. Pylori* tests group GPs were reinstructed for treatment, or were activated for using more *H. Pylori* tests, which resulted in two unknown numbers of less ASD users and in one number of 31% patients that ceased ASD use.[49, 46, 42] The use of more tests caused in one study more endoscopic referrals. The forth study of this group invited patient for a *H. Pylori* test, which resulted in 8% less ASD users.

In the guideline and feedback group GPs held consensus meetings or were given feedback about their prescription policies, but in three of these studies effects on ASD use were not reported.[47, 43, 45] In the fourth study of this group GPs got a prescription protocol and were extensively visited, what resulted in 40% less ASD users.[44]

In general reduction of ASD was not described systematically, but if so studies with multiple active interventions demonstrated better results.

Costs effects From the cohort studies (I) the authorisation program in Canada reported 62% sustained decrease

TABLE 1

Studies included in the Review with specifications of

	Authors, year	Research design	Evidence quality	Study characteristics: Population; i+c gr. (A) Participants (B) Stakeholders (C)
41	Bursey & Crowley, 2000	Dynamic population cohort	B	A: 110.000 residents of NF-land, Canada B: All GPs C: Government
42	Ladabaum & Fendrick, 2001	Prospective multicentre trial.	B	A: P. ulcer patients (54+39) B: PC-centres (3+3), GPs? C: University Michigan
43	Chan & Patel, 2001	RCT	A2	A: All dyspepsia patients B: GPs (133+146); voluntary Hampshire C: Health authority
44	Hurenkamp & Grundmeijer, 2001	RCT,	A2	A: *H. pylori* patients (89/85) B: 48 GP practices, voluntary C: University Amsterdam
45	Weynen & de Wit, 2002	RCT Cluster	A2	A: 260 (99/73/88) patients B: 28 GPs; voluntary C: University Utrecht
46	Banait & Sibbald, 2003	RCT Cluster	A2	A: Practice population (265.000) B: GP practices (57+56); voluntary NW England C: University, GE, Health authorities
47	Jones & Lydeard, 1993	RCT	A2	A: Practice population (500.000) B: GPs (78+101); voluntary; Southampton C: Consensus group GP+GE
48	Allison & Hurley, 2003	RCT	A2	A: ASD patients (321+329) B: Physicians from study C: HMO California
49	Kearney & Liu, 2004	Follow up Cohort	B	A: ASD patients (432) B: GE from study C: MHO Seattle
50	Krol & Wensing, 2004	RCT Cluster	A2	A: ASD patients (63+50) B: 20 GP practices voluntary C: University Utrecht

implementation strategies and efficacy of treatment and costs

Method characteristics: **Intervention type (A)** **Content guideline (B)** **Practical Attributes (C)**	**Implementation strategy**	**Results treatment**	**Results costs**	
A: Authorisation program for reimbursement B: Patient selection for PPI use C: Algorithm for prescription management	I passive	> 80% decrease PPI	PPI < 82% ($1.3 mil) first year; <62% after 2 years ASD <36% ($2.0 mil) first year; <16% after 2 years	41
A: Interactive sessions by GE B: Test & treat strategy C: *H. pylori* serological test for PC	III multiple	32% more tests; same referrals; 31% less prescriptions (p>.001)	79% in intervention group ($ 122 pp) (p=.17)	42
A: Posted guidelines and reinforcement visits by NP B: Management dyspepsia, *H pylori* C: Wall chart, booklet	III multiple	-	5% decrease in medication	43
A: Education of protocol; support by NP B: Tapering prescriptions of ASD by doses and on demand treatment C: follow up patients by NP	III multiple	Decrease of 1,5 PDD; 40% stopped ASD (ns); More HP neg, more H2RA	-	44
A: Education program, financial incentives and personal feedback B: *H. Pylori* diagnosis and treatment C: Dyspepsia questionnaire, HP test	III multiple	17% better follow-up (ns), in incentive group	Less overall costs (€46 pp; ns) in incentive group	45
A: Posted guidelines with education outreach and follow-up visit B: Clinical strategies for referral C: Open access to endo-scopies and serological tests	III multiple	14% more referrals, 4 more tests/ practice	6% more costs ASD	46
A: Consensus meetings GP-SP B: Investigation and refer dyspepsia; appropriate use of guidelines C: reference cards	II single	No difference in referrals and endoscopies	22% more prescribing costs	47
A: Test & treatment random group B: T&T protocol C: Detailed instructions	II single	Less ulcerlike symptoms & abdominal pain; 8% less users of medication	Higher costs because of HP treatment (not hospital)	48
A: Patient Interview and HP test B: Hospital stopped ASD medicine C: Instruction for GPs' review	I passive	71% ulcer; 29% dyspepsia; number stopped?	Hospital $34 less pp; Medication ns; Only ulcer cases	49
A: Direct mail to patients to reduce ASD B: Postal instructions for patients C: Instruction and flowchart	II single	reduction (10% stopped); no change in symptoms and quality	-	50

of costs for PPI.[41] The other cohort study and the one with serological *H. Pylori* tests demonstrated no significant cost effects or did not report calculations.[42, 49]

In the studies with single intervention method (II) the promotion of the dyspepsia protocol resulted in an increase of 22% ASD costs.[47] The other two studies demonstrated by involving patients successful reduction of ASD, but costs effect calculations were not presented.[48, 50]

From the multiple intervention methods (III) three studies demonstrated costs effects varying respectively of 6% increase of ASD costs, no significant changes of overall medication costs until to 5% decrease in medication costs.[46, 45, 43]

Calculation of costs in all studies was not done systematically nor uniform. Sometimes percentages of ASD costs were given, sometimes the absolute costs and sometimes none of the two. Some studies reported overall medical costs, including ASD costs. The different costs calculations are therefore difficult to compare in this review.

Discussion

There is no doubt that radical changes can be reached from a governments' intervention, but when doctors receive a passive mailing or recommendations of key players to pay more attention to prescription protocols the effects on the number of prescriptions and costs are disappointing.[21] Studies with more active intervention strategies that support the doctors with recommendations and visitations had better results.

In studies as identified for this review many of the interventions were concerned with eradication of *H. Pylori*, which resulted in small changes of the number of ASD users or prescriptions. Focussing on positive effects of ASD reduction and related costs two of the three single intervention studies (II) demonstrated positive results. Among the four multiple intervention studies (III) three reported a positive cost reducing effect. On average this implies only a modest effect, comparable to the small effects observed in the earlier

Cochrane reviews on the effects of changes in professional behaviour.[26, 27, 28]

There was only one study that particularly intervened on the gradual termination of unnecessary use of ASD.[14] The GPs were recommended to accompany their patients which resulted in a larger decrease of ASD volumes. However costs were not calculated. The overall conclusion is that the number of high-quality studies on effective interventions for ASD reduction is limited. In addition the incomparable methods applied to calculate prescription rates and costs preclude identification of the most effective intervention strategies. The latter can only be achieved after several studies, including similar outcome measurements evaluating distinct well-defined interventions, have become available.

Only a few quantitative studies evaluated with varying success that ASD reduction requires active intervention strategies with practical instrument for the GP. Grol and Grimshaw already showed the performance phenomenon that actual changes in practice depend on helpful attributes and in particular on attributes that will overcome identified barriers against changing behaviour.[17, 18] More RCT studies on population level have to calculate more thoroughly the effects that appoint to the particular successful instruments. Doctors need rational arguments to get cooperation from patients. As long as side-effects of long term use of ASD are unknown and rebound effects make patients afraid to stop, to negotiate with patients to reduce medication is not an attractive alternative.[12, 24] From this point of view government's interventions like in Canada, which forces cooperation of patients and doctors by financial incentives, seems attractive, but sustainability is questionable.[38] An alternative could be that insurance companies introduce financial rewards, either for the doctor or the patient, to defeat barriers and enforce their negotiations. They possible too could facilitate to combine interventions, both practical instruments and financial compensation, into an effective intervention program of ASD reduction. Evaluation of these multi-interventions have to demonstrate which combinations of instruments fits GPs best.

Conclusion Studies demonstrate that evidence for effective interventions is limited and cost-effectiveness is often difficult to compare. Larger multi-intervention studies with similar outcome measurements and distinct interventions are needed to evaluate the most successful instruments.

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5 Reducing non-evidence based prescription for chronic dyspepsia; a pilot study on a managed care intervention in primary health care

Abstract

Background Acid-suppressive drugs (ASD) are prescribed for 10% of the population each year; 3% are chronic continuous user. Most of these indications are not in accordance with dyspepsia guidelines and gradual reduction or termination is possible.

Objectives We evaluated the implementation of a health insurance company's ASD rationalisation protocol among chronic users in Amsterdam, and analysed the savings on volume and costs of prescriptions.

Method In a cohort study of 2871 patients (>180 DDD ASD, no NSAID), their 158 participating GPs received incentives to follow the protocol. These patients compared to a non-participating group of 267 GPs (control group) without the protocol with 8120 patients. Prescription data was provided by the Agis Health Insurance Company database 2002 - 2004. The number of patients who stopped or reduced ASD was assessed, and standardised outcomes of prescribed volume and its costs were compared in a log-linear regression model.

Results GPs and patients in both groups were comparable in gender, but in the participants group higher in age. After twelve months 141 (5%) of the patients in the participants group had stopped using ASD, against 288 (3.6%) in the non-participants group, demonstrating a difference of 1.4% (0.5;2.3). The volume of DDD had decreased in 41 (1.5%) patients of the participants group while many relapses gave a negative number of 96 (-1.2%) in the non-participants group; in total a difference of 2.7% (2.3;3.1).
Compared to the baseline data in the control group (1.0) the total adjusted OR of the volume of DDD in the participants group was .982. The total cost-adjusted OR was .975.

Conclusion The intervention led to a modest reduction in the number of chronic users, and to a reasonable reduction in volume and costs. An active intervention from the insurance company can stimulate rationalisation of prescriptions.

Introduction

Complaints of reflux and dyspepsia are common; in the Netherlands more than 10% of the population use acid-suppressive drugs (ASD).[1, 2] Most have occasional complaints that soon disappear, but 3,3% uses ASD on a continuous basis.[3, 4, 5] Proton-pump inhibitors (PPI) have proven to be very effective drugs for acid-related complaints and their use increases with 5% per annum.[6] Inevitably the costs of ASD have also risen and currently account for up to 11% of the national pharmaceutical budget.

However, the current widespread continuous use of PPI is not synchronous with the prevalence of severe GORD, which is the only diagnosis for which continuous use is indicated.[7, 8] As the effectiveness of long term PPI use is limited, most dyspepsia guidelines only recommend continuous PPI treatment either for persistent reflux complaints after negative results of a 'test and treat' strategy for *H. Pylori* or for endoscopically confirmed oesophagitis grade C/D.[9, 10, 11, 12, 13, 14] Nevertheless, PPI is frequently prescribed, due to its effectiveness and limited side effects. Even though recent reports indicate a higher prevalence of pneumonia among PPI users, routine iterations of prescriptions are common, creating a drug dependency which is difficult to interrupt.[15, 16, 17] Therefore it can be argued that long term PPI use should be restricted to ensure a more efficient use of health care facilities.[18]

Nowadays health insurance companies support quality improvement programmes in primary care, including pharmacotherapy. In order to stimulate rational ASD prescriptions Agis Health Insurance Company, initiated a managed care project, aiming at improving the quality of prescribing ASD.[19, 20] Earlier analyses of ASD users demonstrated that the efficacy of reduction interventions was highest in the group of continuing treatment users. A large number of these users were able to terminate ASD after a *H. Pylori* 'test and treat' therapy.[21] Many others were able to change their dosage frequency to intermittent or on demand, but instructions to both GP and patients seem to be important in order to achieve reduction.[22, 23, 24]

[25] Especially patient-directed interventions seem to be successful.[←] A protocol based on these results was developed to support GPs in selecting and counselling patients who could potentially reduce [26, 27] their ASD use.[←] A large-scale project was set up which targeted at all the GPs practising in the area of Amsterdam. As passive implementation of prescription guidelines has been demonstrated to be largely ineffective, a strategy was developed with active support of GPs including structured patient information and financial incentives for the participating GPs.[←] [28, 29, 30, 31, 32, 33] We evaluated this practice based managed care prescription project using the database of the insurance company and report the results of the intervention on prescription volume and number of ASD users.[←] [34, 35, 36]

Method

Design All 424 GPs in the Amsterdam region were invited to participate in the project for ASD reduction.

In a controlled, non-randomised, intervention in daily primary care practice, patients of participating GPs (intervention group) were compared to those of non-participating GPs (control group). In a quasi-experimental study-design we controlled for baseline differences in GP and patient characteristics between intervention and baseline period.[←] [37] To find a minimum difference of 5% (α 0.05; β 0.20; two sided) the minimum number of 476 patients in each group was required.

Patients Information about patients and their ASD medication was retrieved from the database of Agis Health Insurance Company. All patients who had been prescribed more than 180 Defined Daily Dose (DDD) of ASD (H2RA and PPI) in the period October 2001 to October 2002 were identified as chronic users of ASD eligible for the project. Patients who had co-medication of more than 30 DDD NSAID annually were excluded. The GP checked the original indication for ASD use of all enlisted patients in the

patients' medical file, and decided whether or not the patient was eligible for the intervention protocol.

Intervention Each GP participating in the project received a so called 'stop protocol'. This package included indications from professional guidelines for rational long-term ASD use, methods to diminish or (gradually) terminate ASD prescriptions, a list of chronic ASD users from the practice and leaflets for patients in different languages. At the kick-off of the project a seminar about dyspepsia management was held for GPs, to explain the approach and aims of the project.
GPs were advised to exclude patients that they regarded as unfit to stop ASD, (high risk for PUD or bleeding, poor physical condition). The GP was free to choose his own method to implement the 'stop protocol' among his patients. As compensation for the time invested three extra consultations could be claimed per patient. Participating GPs were sent an update of ASD prescriptions in their practice every three months, including the actual number of patients who had stopped, or reduced their ASD prescriptions.

Prescription data Until 2006 in The Netherlands 65% of the population below a defined income level had obligatory insurance with one of the health insurance companies. Agis covers 90% of these patients in the Amsterdam region. The Agis Health Database contains medical data on all insured patients including computerised lists of all medication prescribed by GPs. All doses and prices are standard and prescriptions are electronically verified before being saved in the database which is updated weekly. It includes the following data: name, code, dose and price of the drug; prescribing GP, delivering pharmacist, and demographic characteristics of the patient. Data of all ASD prescriptions was collected for analysis in the period September 2002 to September 2004.

Outcome The primary outcome parameter was the number of patients that actually stopped or reduced their ASD use. Patients who stopped were defined as those who had not received a prescription in the last four months prior to the end of the intervention period (Sept. 2004), regardless the type of ASD. This method will exclude patients who relapsed after cessation. Patients that had reduced ASD use were defined as those who reduced the number of DDD in the previous six months with more than 50 percent. To calculate the difference, the number of patients who had stopped or reduced ASD at baseline was compared to the number of patients at the end of the intervention period (the cumulative number of stopped and relapsed).
The secondary outcome was the volume of prescriptions and the costs of prescriptions at group level. The absolute volume of ASD prescription was the total of the number of DDD of all patients whether they increased, decreased or not changed their ASD usage. The accompanying costs of ASD were the total amount paid by Agis to the pharmacist for prescriptions during the project period.

Analysis The data was extracted from the database with Business Objects 6. Analyses were done with SAS-10.1. At first the absolute number of patients that stopped or reduced ASD use were counted and compared between the two groups. Secondly, data in the intervention and control group was standardised. A log-linear model was constructed to control for gender, age, insurance policy and social neighbourhood of the patient, as well as for the GP's gender, age and the size of the practice. Prescription data was analysed eighteen months after the start of the intervention. Prescription data in the non-participants group was fixed to an index of 100%. Prescriptions of patients who died during the project periods or who left the insurance company were excluded from analyses. Then the model calculated the volume and costs of ASD per patient per insurance day, for both the expected and the actual numbers of the intervention and control group. In a multivariate regression analyses the difference between the intervention and

control group was analysed for misrepresentation. The expected and realised decrease of both volume and costs were expressed in a crude and adjusted OR.

Results

GPs' and patients' profile 158 (37%) GPs in the Amsterdam region participated in the project. 2871 patients in their practices were identified as chronic ASD users. The control group (patients from 266 non participating Amsterdam GPs) included 8120 chronic ASD users. Of all ASD users 84% of the intervention group used a PPI compared to 86% of the control group. GPs in the intervention group were older in age than the control group, but of similar gender. ← *table 1*

TABLE 1

Participation of GPs in the Amsterdam region; distribution of gender* and age (%)**

GPs age **	Men		Women		Total
	Intervention	*Control*	*Intervention*	*Control*	
-44	11 (11)	29 (16)	26 (44)	39 (48)	105 (25)
45-54	59 (60)	88 (48)	27 (46)	34 (42)	208 (49)
55+	29 (29)	68 (37)	6 (10)	8 (10)	111 (26)
All	99	185	59	81	424

*p_{gender} = 0.23, **p_{age} = 0.047

During the project 7% of the patients dropped out, both in intervention and control group. Reasons were either death, moving or transfer to another insurance company. No difference in gender of the patients was found after exclusion of drop outs, between the intervention and control group. ← However, there were more elderly and there was a difference of more unemployed and fewer disabled patients in the intervention group, compared to the control group. *table 2*

Effect on number of ASD users ← Table 3 demonstrates the cumulative number of patients *table 3*

who stopped using ASD in the intervention period. Some of these patients stopped initially and then restarted, but in total 141 (5%) of the chronic ASD users in the intervention group completely stopped their ASD use, compared to 288 (3.6%) stopping in the control group, a difference of 1.4% (95% CI: 0.5;2.3).
41 (1.5%) of the chronic ASD users in the intervention group reduced their number of DDD of ASD to less than 50% of the original use. In contrast, during the intervention period the overall number of stopping cases and relapses in the control group exceeded with 96 (1.2%) the baseline numbers that decreased their use of DDD. Therefore the difference in the reduction effect between the intervention and control group was 2.7% (95% CI: 2.3;3.1).

TABLE 2

ASD using patients (>180 DDD) in the Amsterdam region by sex, age and insurance to research groups

		Participants	Non participants
Patients (%)	*> 180 DDD*	*N=2871*	*N=8120*
Sex			
	Men	1243 (43)	3693 (45)
	Women	1628 (57)	4427 (55)
Age			
	-19	5 (4)	18 (5)
	20-39	255 (9)	798 (9)
	40-59	1028 (36)	3110 (38)
	60-69	637 (22)	1771 (22)
	70-79	552 (19)	1469 (18)
	80+	394 (14)	984 (12)
Insurance			
	Work disabled	598 (21)	1866 (23)
	Workers	547 (19)	1686 (21)
	Social insurance	443 (15)	1189 (15)
	Unemployed	1283 (45)	3379 (42)

TABLE 3

Change in percentages (no.) that stopped or decreased ASD use in comparison to baseline in participants and non-participants group

Patients (nr.) [Mar 03-Aug 04]	Participants group	Non-participants group	Difference (95% CI)
Stopped	5.0% (141)	3.6% (356)	1.4% (0.5; 2.3)
< 50% DDD	1.5% (41)	-1.2% (-96)	2.7% (2.3; 3.1)

TABLE 4

Volume effect (DDD) and Costs effect (€) of ASD in participants group compared to non paticipants group; adjusted OR and CI 95% from multivariate analysis

Number and Euro	Absolute difference	Crude OR	Adjusted OR	CI 95%	Adjusted difference (/patient/year)
DDD	80,909	0.95	0.982	0.979; 0.985	40,062 (9.30)
Costs	314,443	0.85	0.975	0.972; 0.978	46,545 (10.80)

Effect on ASD volume and costs

During the intervention period the total prescription volume dropped from 103.5 to 102.5 percent in the intervention group compared to 100% in the control group. The absolute decrease of the volume was 80,909 DDD, 14% of the volume at the start of the intervention.← *table 4* Following adjustment to allow for pre-intervention differences from the log-linear model, the crude OR (0.95) of the intervention and control group became 0.98. The adjusted decrease of the volume, after controlling for the group differences (higher age of GPs and patients as well as the higher number of unemployed patients in the participants group) was 40,062 DDD.

To analyse possible cost-saving the prescription costs per patient per insurance day were calculated. Costs in the intervention group decreased from 104 to 102 percent; 2% more than in the control group, causing an absolute decrease of € 314,443.← *table 4* The crude OR of the difference was 0.85, but adjusted for pre-intervention differences and changes of price indexes the OR was 0.97. The adjusted absolute decrease in costs reached up to € 82,024.

Discussion

This health insurance company initiated managed care ASD rationalisation programme had a modest effect on prescription volume and costs. An additional 1,4% of the patients in the intervention group stopped ASD use, and 3% of the patients reduced their number of DDD of ASD intake, compared to the control group. The total volume of ASD prescriptions was reduced by 1.8% resulting in a drop in costs of 46,500 €. When the financial incentive for the GPs (24,375 €) is taken into account the net cost-savings were only half this amount.

Although we observed only a small effect size, our results confirm those of other audit and feedback studies.[38] Hurenkamp and Krol et al demonstrated that 15-25% of the patients could stop using ASD with intensive support from their GP.[20, 25] Despite intensive feedback in our study, there was only a minority of the eligible patients in our study that stopped. This could be explained by several factors. We conducted multiple intervention using feedback information and financial incentives. However active support for GPs was limited because communication with the participating GPs was only on paper and not face-to-face. Large scale intervention like ours do not allow for intensive personal contact with GPs in real life setting. As the GPs were not randomised, those participating might have been more motivated to reduce ASD. This selection bias is illustrated by the fact that participants already had a fewer number of ASD using patients at baseline than that of the non-participants (18 versus 30), possible as a result of a more rational ASD prescription policy re-existing. Therefore they may have had more 'indicated' and 'heavily addicted' ASD users who could not be included in the protocol.

Assimilation bias was also possible when associates in their practices or other GPs in their district, will have used the 'stop protocol' also. Furthermore at the start of the intervention there was a public discussion about PPI being a life-style drug. During that period the government negotiated with pharmacists about the prices of PPI

which led to 40% price reduction. This may have motivated non-participating GPs towards a prescription policy to reduce ASD. Finally all chronic ASD users were eligible for the study cohort (with exception of NSAID use), regardless of other characteristics of the patients. The decision about the eligibility of the patients for the stop protocol depended on the clinical judgement of the GPs. Those patients who did meet the criteria for long-term use will not have been approached. It was to be expected that GPs would exclude more than 50% of chronic ASD users, because they were older patients (>60y), many of whom use ASD as part of poly-pharmacy which make it more difficult to change behaviour in drug use. We believe that one of the major differences with other multiple intervention studies is that the GP's support for patients who tried to stop ASD was limited. Insufficient active support of the GPs could have resulted in more relapses. It is possible that merely using a financial compensation of extra fees to motivate GPs, as in this study, is not enough to create major effects; other barriers that may obstruct GPs from altering prescriptions need to be identified.[39, 40] In future research strategies using active involvement of patients should be explored, and the effectiveness of drug prescription programmes should be established in large-scale randomised designs.

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ACCEPTED AS:

Patient attitudes towards and experiences with an intervention programme to reduce chronic acid-suppressing drug intake in primary care

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6 Patient attitudes towards and experiences with an intervention programme to reduce chronic acid-suppressing drug intake in primary care

Abstract

Objective Many patients are using Acid-Suppressing Drugs (ASD) unnecessary. An insurance company initiated intervention programme aiming at reduction of chronic ASD use, was introduced in PC-practices. We evaluated the attitude and experiences of the participating patients.

Methods A survey was conducted among a random sample of 2376 long-term ASD users using a validated questionnaire that combined CAHPS and QUOTE methodology. Using a psychometric principal component analysis we assessed the role of GPs in three scales: quality of support; communication and conduct; involvement in decisions. Both the importance of and experiences with quality items, transformed into quality impact indices, were measured.

Results Of 2376 questionnaires distributed, 1808 (76%) were returned, 1270 (54%) were valid. 188 were of patients that participated in the programme. The majority was dissatisfied with the GPs' support: no information about rebound side effects (76%), lifestyle habits (68%), and reasons to stop (50%). Compared to the non-participants 9% more participants stopped ASD use (p=0.04).

Conclusion A majority of patients on chronic ASD was prepared to participate in the drug-reduction programme. Although 16% succeeded in stopping ASD use, the majority was dissatisfied with the role of the GP. Improved GP support might have make more patients stop using ASD.

Introduction

Dyspepsia is very prevalent in the community and acid-suppressing drug treatment accounts for 10 percent of the pharmacy budget. Three percent of all patients using acid-suppressive drugs (ASD) are long-term consumers.[1, 2, 3] Most prescriptions are for proton-pump inhibitors, and the number of these prescriptions increases annually by 5%.[4, 5, 6] Many patients, in particular those with recurrent complaints who have been referred to a specialist, believe they have to use medication for the rest of their lives.[7, 8] Actually, the indications for chronic ASD use are limited and many of the present consumers could stop or taper their use to either on demand or intermittent use.[9, 10, 11, 12, 13] In order to increase the efficient use of health care resources antacid drug reduction programmes, based on evidence based guidelines are implemented in general practice.[14] Patients however, have little motivation to reduce ASD use, because the treatment is very effective in suppressing dyspeptic symptoms. In general, patients do have concerns about safety and side effects of drugs, but most of them do not perceive the need for cost-effectiveness.[15, 16, 17, 18, 19] The effectiveness of most ASD cessation programmes is limited, mainly due to the fact that the patient's perspective is inadequately considered in the intervention. Patients will use behavioural strategies to influence the prescribing physician not to change the successful drug regimen.[20, 21] Active multiple-intervention methods, that focus on doctor-patient communication and pay attention to the patients' requirements and expectations, are necessary.[22, 23, 24, 25, 26, 27] If GPs were more aware of the patients' need for counselling on the background and rationale of chronic ASD use and the need for cost-effectiveness, they could encourage patients to experiment with ASD use to find the lowest effective dose, thus contributing to effective drug use.[28, 29, 30] Agis, a major public health insurance company in The Netherlands, conducted a regional managed care project to stimulate rational ASD prescription, combining guideline implementation with active support of patients. Participating GPs received a 'stop protocol' based on Dutch dyspepsia guidelines, together with a list of patients on chronic ASD in their practice.[31, 32, 33, 34] The GPs selected the patients

they considered eligible for the programme, and counselled and supported them in their cessation process. Every three months the GPs received feedback on the ASD consumption among their patients (stop/success rate). As compensation the GPs were allowed to charge additional consultation fees for their efforts.

We evaluated the effect of the ASD reduction programme from the patients' point of view, and analysed the attitude of participants towards the initiative and their experiences with the implementation of the programme.

Methods

Design In a postal survey questionnaires were sent to long-term ASD users.

Patients Long-term ASD users were selected from the Agis prescription data warehouse, which contains information of 1.5 million patients in the central region of the Netherlands. A random sample of 2376 long-term ASD users was taken from all practices in the region where the reduction programme was implemented. Eligibility criteria were: resident in Agis' primary region, using at least 180 defined daily doses (DDD) of ASD in the last year, and no chronic NSAID co-medication. All eligible patients received a postal questionnaire analysing their attitudes towards the intervention programme and their experience with the cessation process.[35, 36, 37]

Questionnaire development An 'ASD questionnaire' was developed based on an existing general questionnaire, the CAHPS (Consumer Assessment of Health Plan Survey) combined with elements of the QUOTE (QUality Of care Through the patient's Eyes) surveys.[38, 39, 40, 41] The questionnaire contained general items about dyspepsia, taken from the CAPS questionnaire and of subjective-specific items about perceived importance of quality in care, derived from the QUOTE methodology. In addition,

interviews were held with patients who participated in the programme, as well as with a few key coordinators of the programme. Based on these interviews, questions about quality aspects from the patient's perspective about reduction of ASD were formulated and added to the questionnaire. In two successive sections respondents were asked to indicate the importance of quality aspects and their experiences in the programme.
In the questions about experiences ASD consumers were asked about the frequency with which quality criteria had been met, using a 4-point Likert scale (never, sometimes, usually and always). Finally, statements were formulated about the role of the GP and the health insurer in the managed care project. On a scale from zero to ten, (0 being lowest and 10 the best possible), they could rate their satisfaction with their GP and the health insurer.

Questionnaire validation To validate the questionnaire a psychometric analysis was performed. As a result of the principal component analyses with varimax rotation, three scales were constructed, based on the experiences with quality aspects. After validation of the three scales, the major themes in the questionnaire were: support given by the GP; information from and conduct of the GP; involvement of patients in the process. These themes refer, within the framework of the ASD reduction programme, to the GP's intervention activities.

Analyses The average score for both the experience and the importance items were analysed. The multiplication of both factors (using the importance scores as weighting factors) provides a figure which indicates the improvement score of important areas in the intervention; the quality impact index.[42] ← In general, high impact indices coincide with bad experiences and, with scales ranging from one to four, the worst impact indices will be 4x4. A score of eight or above was arbitrarily regarded as indicating a need for improvement.

Chi-square tests were used to compare the characteristics of the participants in the reduction programme with those of non-participants. The percentage of respondents who agreed with the statements about the role of the GP and the health insurer was calculated. Agreement was achieved when respondents indicated that they either 'completely agreed' or 'agreed'. Analyses were done using SPSS 14.0.

Results

Respondents Of the 2376 questionnaires randomly sent to eligible patients 1808 (76%) were returned. Of these 420 questionnaires were returned incomplete, 53 of the respondents were not insured with Agis, 20 had not used PPI in the last two years and 45 questionnaires were filled out by a third person. Of the 1270 (54% of total) remaining valid questionnaires, 229 (18%) patients actively participated in the ASD reduction programme. Some of them did not answer all the questions about their ASD consumption, which left 188 (16%) of the valid questionnaires of patients that participated in the programme for analyses and 977 valid questionnaires of ASD users that did not -participate in the programme. Patients' gender, age and education in the two groups were comparable. ← *table 1* In the participating group, the ASD medication was more often prescribed by the GP than the specialist ($p<0.001$) and 11% more of them ($p<0.01$) experienced their health as good or very good compared to the non-participating group. In both groups about 80% used PPIs, and 20% had had an endoscopy in the past.

Outcome of the intervention programme After completion of the reduction programme 30/188 (16%) of those who participated completely stopped ASD. ← *figure 1* In the non participating group 65/977 (7%) completely stopped ASD (diff. 9%, $p=0.04$). Participants that stopped ASD intake and those who did not, were comparable in gender and age. Both groups used the same proportion of PPI and H2RA. Whether they stopped using ASD or not, more than half of the participants indicated that they

TABLE 1 **Characteristics of study population in %**

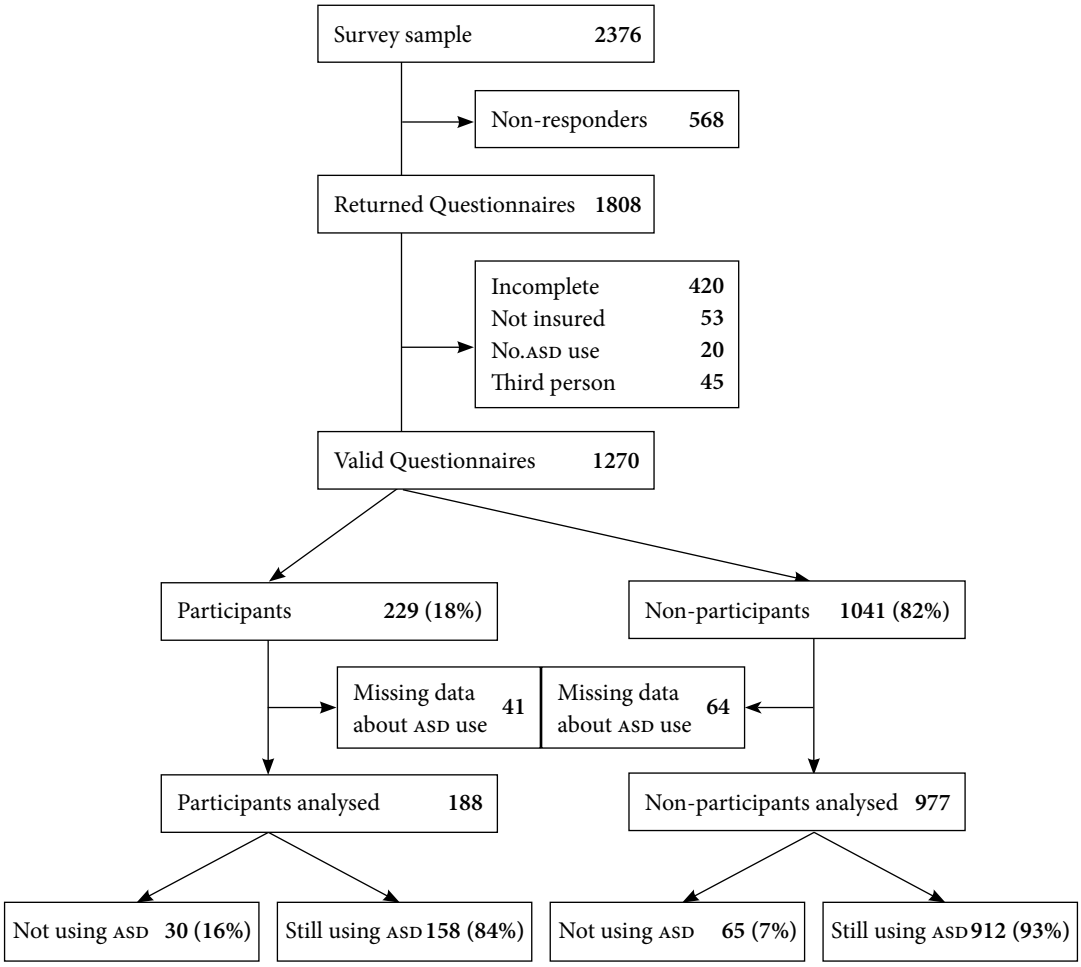
		ASD users (n=977)	ASD users in the reduction programme (n=188)
Gender			
	Male	40.7	41.7
Age			
	25-54	25.6	30.1
	55-74	51.9	47.7
	75+	22.3	22.5
ASD prescribed by **			
	GP	66.7	87.5
	Specialist	29.1	10.9
	Other	4.2	1.6
Education level			
	Low	64.7	63.3
	Moderate	25.4	28.3
	High	9.5	8.3
General Health *			
	Very good	5.9	11.4
	Good	39.6	45.1
	Acceptable	45.1	36.4
	Bad	9.4	7.1
Antacid Use			
	PPI	82.1	79.3
	H2RA	17.9	20.7
	Endoscopy	21.4	19.6
Health compared to the previous year			
	Better	16.3	20.0
	Same	54.1	56.2
	Worse	29.6	23.8

*p<0.01
**p<0.001

were in reasonable or good health. Of those who stopped, 33% felt that they were healthier than a year before.

Attitude towards the programme More than 70% of the patients indicated that they neither had a problem with being approached for the reduction programme, nor with the participatory role of the health insurance company in it. Of the patients included in the ASD cessation programme 72% was approached during consultation with the GP. After they agreed

FIGURE 1 **Diagram of respondents with chronic ASD use and the number that participated or did not in de ASD reduction programme**



to participate and stop ASD, 11% of the participants did not consult their GP again and 48% visited their GP only once more. Patients participating in the programme also stated that their GP rarely or never elaborated on the reasons to stop ASD (50%), did not promote dietary or lifestyle changes to support ASD cessation (68%), and did not discuss the possibility of rebound effects after cessation (76%). When asked to rate their satisfaction with the role of the different parties in the programme, the respondents gave the GP an average

score of 8.0 (SD=1.7) and the health insurer an average score of 7.5 (SD=1.8).

Evaluation of the programme The patients who participated in the reduction programme were asked about their experiences and to evaluate various quality aspects. Of the 188 participants 173 (92%) answered all the sub-questions on these items. The first column in table 2 demonstrates that 'quality of GP support during the attempt' scored 2.9 which is a low score indicating a general negative experience. ← From the patient's perspective, 'quality of GP support' is more important than 'communication and conduct by the GP' and 'patient involvement in decisions'. The latter aspects scored respectively 1.5 and 1.6 on a scale from 1 (good experience) to 4 (bad experience). The 'importance' score of those two scales in column two demonstrates relatively minor differences (± 3.2). Combining the two scores of experience and importance of quality gave an 'improvement' score of 8.6 for the first scale 'Quality of GP support during the intervention'. The 'experience' score in contrast to the importance score of the second scale 'Communication by conduct of the GP' and the third scale

table 2

TABLE 2

Experience and importance scores of patients on ASD that participated in the reduction programme and the quality impact indices on the three scales. (n=173)

	Experience score *	Importance score**	Improvement score***
Quality of GP support during the intervention	2.89	2.98	8.6
Communication by and conduct of the GP	1.52	3.23	4.9
Patient involvement in decisions	1.59	3.25	5.2

* 1=very good experience, 4= very bad experience
** 1=not important, 4=of the utmost importance
*** Maximum score is 16

'Patient involvement in decisions' were relatively low and resulted in an average improvement score of 5.

Discussion and Conclusions

Summary of results In contrast to the general opinion there seems to be sufficient public support for insurance company initiated ASD reduction programmes, implemented in cooperation with GPs. The majority of long-term ASD users were happy to be approached and were willing to cooperate in a drug reduction programme. In this study 16% of the ASD users who were invited to participate in the programme, succeeded in stopping ASD use. One third of those patients who managed to stop using ASD reported that their health had become better than in the previous year.

Discussion The results of this study demonstrate that the group of patients on ASD that participated in the programme was only a smaller subgroup of those eligible. Compared to the non participants the participating group more often received treatment from the GP and did experience a better health.← Possibly GPs selected mainly those patients for whom they thought it would be less difficult for them to cease ASD use, without intensive GP support. This implies that a larger group of long-term ASD users could succeed in stopping ASD use with an increased supportive effort of GP's. In our evaluation many patients experienced a lack of adequate support from their GP after entering the programme; they did not receive sufficient follow-up consultations (over 50% had only one extra consultation) and were not optimally informed about the benefits of reducing ASD.

table 1

Focusing on the practical aspects of the programme, the results demonstrate a clear need to combine optimal motivation of the patients with strong GP support. Patients should not only be encouraged to try to reduce ASD use, but they also need support to help them to continue to reduce dependence on ASD (lifestyle habits

and rebound side effects) and to sustain their independency of ASD use (on demand or intermittent use) thereafter. The fact that GPs fail to provide that support, could simply be due to poor time management by GPs, but it is more likely that the GPs do not have adequate tools to provide the necessary level of support. In any future reduction programmes, GPs should be provided with specific tools to support their patients during the process of reducing drug intake.

From this point of view the limitations of the intervention programme become clear. Instead of approaching any patient who met the eligibility criteria for the programme, the selection was completely left to the GPs clinical judgement. The GP may have anticipated on the chance of successful reduction by including fewer "difficult" patients, knowing that lack of patient cooperation and lack of time to actively monitor patients could lead to failures or relapses. GPs' own assessments of their patients, therefore, may have had a biased influence on the outcome.

Practice implications The practical conclusion is that patients need more supportive interaction with the physician during the drug rationalisation programmes. This kind of support however, could also be provided by others. A nurse practitioner or pharmacist, for example, could act as intermediary in the programme to provide more support in the reduction process.[43, 44] This intervention strategy would extend the role of the insurance company, which in the present design only offered passive and financial support for enrolling ASD users in the programme. The question remains what better instruments GP's should be given to actively support their patients. Should the insurance company include preconditions for these instruments when introducing programmes for disease management in order to improve success rates?

In conclusion, the managed care reduction programme will be successful for a percentage of long-term ASD users. This percentage

might increase if patients received better support from their GPs. Better conditions and tools for disease management should be developed and offered to GPs to help them to encourage their patients to stop or reduce ASD use.

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SUBMITTED AS:

A health insurance company-initiated multi-faceted intervention for optimising acid-suppressing drug prescriptions in primary care; a randomised controlled trial

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7 A health insurance company-initiated multi-faceted intervention for optimising acid-suppressing drug prescriptions in primary care; a randomised controlled trial

Abstract

Objectives To evaluate the effectiveness of a health insurance company-initiated intervention strategy aimed at optimising acid-suppressing drug (ASD) prescription in primary care.

Design A cluster randomised controlled trial.

Setting and background 112 GP peer review groups (993 GPs) in the central region of the Netherlands were randomised.

Intervention GPs in the intervention group received a standard 'stop-protocol', a list of their patients on chronic ASD, and financial compensation for additional consultations with these patients. GPs in the control group did not receive any of these interventions.

Participants Prescription data of 23,433 patients were extracted from the database of the regional health insurance company.

Main outcome measures Proportion of patients that reduced ASD consumption by more than 50% and changes in annual volume and costs of ASD prescription. Differences in ASD reduction and in volume were analysed applying multilevel regression analyses.

Results At baseline 2.4% of the patients (n=967,506) of the participating practices used ASD chronically (>180 DDD annually). During the six-month intervention 14.1% of the patients in the intervention group reduced ASD compared to 13.7 in the control group (adjusted RR = 1.04, 95% CI 0.97;1.11). Changes in intervention and control group in mean volume per patient of ASD prescription were similar (β=0.33 DDD, 95% CI -3.0;3.6).

Conclusion A health insurance company-initiated multifaceted intervention, including practical tools and financial incentives, did not alter ASD prescription practice in primary care. More tailored interventions, including patient-targeted initiatives are required to optimise ASD prescription.

Introduction

Acid-suppressing drugs (ASDs) are among the most frequently prescribed drugs; up to 10% of the population uses H2-antagonists or proton pump-inhibitors (PPIs) on a regular basis.[1, 2, 3] In most European countries the use of ASDs, especially that of PPIs, is growing annually.[4, 5] ASDs generally offer a prompt and effective reduction of acid related symptoms.

More than one third of all patients on ASDs use more than 180 defined daily doses (DDD) annually, suggesting chronic drug use, yet there are only few indications for continuous ASD prescription. Moreover, an increased risk of both pulmonary and gastrointestinal infections, as well as osteoporosis was reported in patients chronically using PPIs, but these reports did not change PPI prescription habits.[6, 7, 8, 9] Most current guidelines recommend continuous acid suppression only in case of oesophagitis grade C and D or in case gastric protection is required in patients using NSAIDs.[10, 11] Most patients with symptoms of gastro-oesophageal reflux disease (GORD) or dyspepsia will experience symptom control on a so-called 'on demand' or 'intermittent' regimen of 1-2 weeks of ASD prescription. In clinical practice, it proves difficult to limit patients in their ASD consumption. Drug dependency is maintained by both the (perceived) effect on acid related symptoms and the prompt acid rebound effect that follows cessation of the drugs.[12, 13, 14, 15, 16, 17]

In most western countries about 10% of the national pharmaceutical budget is spent on ASDs.[1] Cost-effectiveness of ASD prescription could be substantially improved by limiting chronic prescription of ASDs in clinical practice and changing continuous into on-demand regimens. Primary care should be the main focus, as most of the ASDs are prescribed by general practitioners (GPs). To date, compliance with clinical practice guidelines for dyspepsia proves difficult to achieve without supporting interventions.[18, 19]

Many studies have demonstrated that an active multi-faceted strategy may be effective in implementing clinical guidelines. In such a strategy each practice setting requires tailored interventions,

based on the barriers that GPs experience during implementation.[20, 21] To improve compliance with guidelines, this strategy should be integrated into routine practice, complex changes should be avoided and practical support should be offered.[22, 23, 24, 25, 26] Financial incentives are also suggested to improve compliance with clinical guidelines, but their effectiveness in optimising ASD prescription has not been assessed in prospective research.[27, 28, 29]

Agis, a major health insurance company in the Netherlands, initiated a multi-faceted intervention program aiming at optimising ASD prescription in primary care.[30, 31, 32] We report the effectiveness of this managed care program, which included financial incentives, on volume and costs of ASD prescription.

Methods

Study design and setting A cluster randomised controlled trial was conducted in the central region of the Netherlands. In this area Agis health insurance company enlists more than 1.5 million patients. All GPs in the region with more than 250 patients insured with Agis (N=993) were selected to participate in the programme and were randomly allocated to either the intervention or to the control group. Due to the presumed interaction between cooperating GPs, we choose to randomise at GP peer group level.

Intervention GPs in the intervention group received a so called 'stop-protocol' by mail. This package included: 1) instructions for rational ASD prescription according to current professional guidelines; 2) suggested strategies for (gradual) withdrawal of ASDs; 3) an updated list per practice of the patients on chronic ASD use; and 4) patient information letters about rational ASD use in different languages. Further implementation of this 'stop protocol' was left to the GP. As compensation for their efforts to change ASD prescription, GPs were granted three extra consultations (in total € 75.-) for each patient included in the 'stop-protocol'.

Every three months during the intervention period GPs received an updated list of their patients on chronic ASDs, and those who reduced ASD medication.

Control group In the control group, care was provided as usual. GPs did not receive the stop protocol, nor were they informed about the chronic ASD users in their practice. They did not receive financial reimbursement for efforts to reduce chronic ASD use in their patients.

Measurements The Agis Health Database (AHD) contains computerised prescription data of all enlisted patients. The AHD is updated every month and includes name and demographic characteristics of the patient, ATC code, dose, amount and price of the drugs, prescribing GP and delivering pharmacist. Chronic ASD use was defined as a use of more than 180 defined daily doses (DDD) of ASDs (H2 receptor antagonists or PPI) annually. Patients with co-medication of more than 30 DDD of NSAIDs were excluded, because of the possible need of gastro protection.[10]

The volume of ASD was defined as the mean number of DDDs per patients. Subsequently, mean costs of ASD per patient were calculated. Costs were fixed on the drug price level at the start of the program. Baseline ASD prescription during the six months before the intervention was categorized according to the average number of DDD per prescription per GP; < 90, 90 to 180, or >180 DDD. Patients were categorised in Moroccan, Turkish or "other" ethnic background. Patients were further categorised as employees, work-disabled, unemployed and those receiving social insurance. Urbanisation of the practice population was categorised as urban (high), suburban (median) and rural (low).

Outcome The primary outcome parameter was the proportion of patients that reduced ASD use by at least 50% during the first six months of the intervention, compared to the average number of DDD that the patients used in the six months before the

intervention. Secondary outcome parameters were the change in mean number of DDD per patient and mean costs of ASD medication per patient during the first six months of the intervention.

Data analysis Chi-square tests were used to compare baseline characteristics of GPs and patients in the intervention and control groups. To assess the effects of the 'stop-protocol' on ASD reduction, a multilevel Poisson regression model was used, reporting the relative risk (RR) for the percentage of responders. The effect of the intervention on DDD and costs was assessed in a multilevel linear regression model, reporting the regression coefficients of the differences in changes between the two groups. In both multilevel models, data were analysed at GP practice and at GP peer group level. The full multilevel models of both analyses were performed with DDD per prescription at baseline as a random effect variable, together with fixed effect variables such as gender, age, ethnicity, insurance groups and urbanisation level of the patients, as well as gender, age and the size of practice population of the GPs. Relative risk (RR) and regression coefficients (β) are reported with 95% confidence intervals (95% CI).

Results

Baseline characteristics The intervention group consisted of 61 peer groups with 559 GPs, the control group of 51 peer groups with 434 GPs. Mean ages of the GPs and the prescription rate at baseline did not differ between the two groups.← *table 1*

Of the 967,506 enlisted patients in the participating practices 2.4% were on chronic ASD use. Patients on chronic ASD in the intervention group (12,841) did not differ in gender (59% female), nor in age or income status compared to those in the control group (10,592).← *table 2*

The mean number of patients on chronic ASD per 1000 patients was 24.2 in both groups. On average they were prescribed 206 DDD of ASD in the six months prior to the start of the trial. In both groups

TABLE 1

Participating GP peer groups in the intervention and control groups, characteristics of patients and GPs (%)

		Intervention	Control	P-value
Peer Groups		**N=61**	**N=51**	
Age GP (mean)				0.73
	<45	52	59	
	45-55	43	35	
	>55	5	6	
Urbanization practice				0.97
	Low	25	24	
	Mean	18	20	
	High	57	55	
Mean Age practice population				0.13
	<55	8	6	
	55-59	11	25	
	60-64	56	57	
	>64	25	12	
Mean DDD per prescription				0.26
	<90	9	37	
	90-180	49	63	
	>180	2	0	

TABLE 2

Characteristics of patients using more than 180 DDD ASD annually in intervention and control group (%)

		Intervention	Control	P-value
Patients (%)	**> 180 DDD**	**N=12841**	**N=10592**	
Gender				0,32
	Men	41	41	
	Women	59	59	
Age				0.051
	-15	.2	.1	
	15-44	15	16	
	45-64	40	41	
	65-80	34	33	
	80+	12	11	
Social status				0.24
	Work-disabled	19	19	
	Employees	26	26	
	Social insurance	8	8	
	Unemployed	47	46	
Ethnicity				0,001
	Moroccan	5	4	
	Turkish	3	4	
	Others	92	92	

8% of the patients were lost to follow-up after implementation, mainly due to switch to another insurance company.

Difference on chronic ASD users In the first six months after the implementation of the 'stop protocol', 1,812 (14.1%) of the patients on chronic ASD in the intervention group reduced their ASD by at least 50%, compared to 1,456 (13.7%) in the control group (RR 1.02, 95% CI 0.95;1.09).← After

table 3

TABLE 3

Proportion of responders, mean volume (DDD) and costs (€) of ASD prescriptions per patient(p/p) before and after intervention in and differences between intervention and control group (95% CI). Relative risk (RR) of responders and regression coefficient (β) of difference in mean volume (DDD) and mean costs (€) of ASD prescription per patient (p/p), between the intervention and control groups, after adjustments from multivariate multilevel regression analyses. Poisson model for RR and Linear model for β (95% CI)

6 Months period	Responders (<50% DDD)	DDD p/p Pre-intervention	DDD p/p Intervention	Costs p/p Pre-intervention	Costs p/p Intervention
Intervention group (n=12,841)	14.1% (1,812)	206.1	210.2	164.1	165.8
Control group (n=10,592)	13.7% (1,456)	206.8	210.9	161.1	163.2
Difference (95%CI)	0.4% (-0.63;1.43)	0.7 (-4.5;3.2)	0.7 (-4.2;3.0)	1.7 (-1.9;5.3)	2.1 (-1.7;5.9)
Crude RR and β (95%CI)	RR = 1.02 (0.95 ;1.09)	β = -0.57 (-6.5 ; 5.4)		β = 5.50 (-8.4 ; 13.8)	
Adjusted RR and β (95%CI)	RR = 1.04 (0.97 ;1.11)	β = 0.33 (-3.0 ; 3.6)		β = 1.63 (-1.3 ; 4.5)	

Multilevel analyses were performed as follow: 1) Multivariate simple analyses, adjusted for peer group clustering, 2) Multivariate baseline, adjusted for peer group clustering and mean difference of DDD of GPs in pre-intervention period, 3) Multivariate full model, adjusted for peer group clustering, DDD at baseline and case-mix, including sex, age, urbanisation, ethnicity, social status of patient and sex, age, number of patients of GP.

adjustment for GP and peer group clustering and case-mix variables in the full model, the RR was 1.04 (95% CI -0.97;1.11). ← *table 3*

Difference in ASD volume and costs In the intervention group, the mean prescription volume per patient rose from 206.1 DDDs in the six months before to 210.2 DDD in the six months after the introduction of the intervention. In the control groups, the volume rose from 206.8 DDD to 210.9 per patient. There was no difference between the changes in both groups in DDD per patient. ← *table 3* This did not change after correction for prescription rates at baseline and for the full multilevel model of GP and peer group clustering (β=0.33; 95% CI -3.0;3.6). ← *table 3* The mean costs of ASD prescription per patient in the intervention group rose from 164.1 Euros in the six months before the intervention to 165.8 Euros in the six months after the intervention. In the control group, the mean costs for ASD per patient rose from 161.1 Euros to 163.2 Euros. The difference in the changes in costs between both groups was 0.4 Euro (95% CI -3.41; 4.21). ← *table 3* Multilevel analyses showed similar findings: β=1.63, 95% CI -1.3;4.5). ← *table 3* Including the costs of the financial incentive (€ 12.- per patient) the additional costs of the intervention were estimated at 15 Euros per patient per year.

Discussion

This managed-care ASD health insurance company initiated rationalisation programme did not reduce ASD prescription rates both the number of patients on ASDs and the volume or costs of antacid drugs were similar in the intervention and control group. These results confirm earlier reports that simply introducing a 'stop protocol' and giving feedback information to physicians is ineffective in influencing routine prescription practice. ← *33*

Comparison with other studies Hurenkamp and Krol demonstrated that after intensive individual support of both patients and GPs, 10-15 percent of the patients could stop using ASD. ← *13, 34* Most studies in an earlier

systematic review of our group on the effectiveness of ASD reduction programmes did not demonstrate an effect of the interventions on ASD consumption.[35] In contrast some studies reported an increase in ASD use after expert visits to the GPs. In the design of our trial we assumed that simply distributing evidence-based prescription guidelines to GPs is an ineffective implementation strategy.[20] By combining this with practical attributes and financial incentives we expected an improved compliance of GPs to prescription guidelines and a greater impact of the programme on ASD prescriptions.[28]

A number of factors might explain the lack of effect observed in our trial. The duration of the intervention might have been too short. The time required to switch from a continuous to an on-demand or intermittent ASD prescription regimen has not been studied adequately, but a prolonged follow up might result in a more positive effect.[31, 33] Some GPs consider the initiative as a mainly economically driven programme of the health insurance company to alter their prescription policy. Sending them the 'stop protocol' by mail may have been ineffective in increasing their motivation any further, and may have resulted in a rather passive contribution of at least some of the participating GPs. The focus in the intervention was mainly on the GPs, and we may have underestimated the role of the patient in the programme. Given the drug dependency of patients on ASD, GPs may have had problems convincing the patients to change their drug regimen.

Strengths and weaknesses This is the first study in which a health insurance company initiated an intervention program is evaluated using a randomised controlled trial design.[35] The conclusions are quite robust given the validity of this design, while the generalisability of the findings seems warranted because all GPs in a large region in the Netherlands participated in the implementation of the programme. Due to its economic function and the systematic collection process the prescription data in the AHD are likely to be complete and accurate.

The lack of effect may also have resulted from an unexpectedly large number of patients in the control group that reduced ASD. At the time of our study a public discussion about the status of ASD as a lifestyle drug was ongoing, leading to government-initiated cuts on ASDs prices and changes in reimbursement policy. This may have made GPs in the control group more aware of the societal impact of ASD prescription, resulting in a drop in ASD prescriptions in some patients. Because overall ASD prescription rates in the control groups increased during the study period this effect is likely to be small.

We left the inclusion of patients completely to the GPs. At the start of the programme all chronic ASD users in the participating practices (with exception of NSAID users) were considered eligible for the intervention. We anticipated that GPs would exclude more than 50% of the chronic ASD users, as they considered it too difficult for the patient to change the drug regimen. The low number of responders may be an indication that GPs selected only the small proportion of patients whom they presumed to be able to reduce ASD use without much additional pressure. Instead of leaving the selection process to the GPs, direct approach of eligible patients by the research team might have resulted in a beneficial effect of the intervention strategy.

In a pragmatic study like this, in which the intervention is closely related to daily practice, there is no detailed insight in the motivation of the GPs or in the responses of the patients. Though all GPs were adequately informed beforehand, the protocol was sent to them without asking cooperation individually. Some GPs may have disregarded participation immediately, while others actively participated. This varying participation rate obviously will have affected the number of ASD patients included and the observed effect of the intervention.

Conclusion This health insurance company initiated managed care programme to optimise ASD prescription did not result in a reduction of ASD prescription in primary care. Although

this might be attributable to the fact that GPs do not want health insurance companies to interfere with professional prescription policies we tend to think that this managed care programme did not adequately address the problems that GPs face in changing prescription patterns of an effective drug in a patient group satisfied with their drug regimen. A multi-faceted intervention not only including practical attributes and financial incentives, but also interventions tailored to the patients as well as the problem under study.[21, 22, 23] may be more successful. In the case of ASD prescription, probably not only the prescribing physician, but also the patient needs to be convinced of the benefits of antacid drug reduction. More research is required to find out how this can be achieved.

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A structured intervention for optimising acid-suppressing drug therapy in primary care; which strategy is most effective?

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8 A health insurance company-initiated multi-faceted intervention for optimising acid-suppressing drug prescriptions in primary care: structured practice support does improve outcome

Abstract

Introduction Acid-suppressing drug (ASD) consumption continues to increase, but prescription is often not in accordance with current dyspepsia guidelines. To improve cost-effectiveness of ASD consumption in primary care a multi faceted intervention programme was initiated by a health insurance company. Since changing ASD prescription policies proved to be difficult for GPs, supplementary support was offered by practice facilitators.

Aims and methods In a sequential, randomised controlled trial we evaluated the effectiveness of two intervention strategies, telephone support (TS) or practice visits (PV), in reducing ASD prescription in primary care. A total of 434 GPs in 51 GP peer groups in the central part of the Netherlands were invited and 90 GPs participated in the program. The GPs were randomly allocated to one of the two groups. The GPs allocated to the telephone support (TS) group received repeated telephone support and a "stop protocol" during the first 6 months, but no intervention during the 6-12 month period (when they served as the control group for the practice visit (PV) intervention). Those allocated to the PV group received no intervention during the first 6 month period (during which they served as the control group for the TS intervention), but received practice visits and a "stop protocol" during the 6-12 month period. Both the TS and PV interventions were carried out by practice facilitators. Detailed prescription data were extracted from the Agis health insurance database. The primary outcome measure was the proportion of patients that actually reduced ASD intake (responders). Differences in responders and in volume were analysed using multilevel regression analysis.

Results At baseline 3424 patients in the participating practices used ASD on a chronic basis, with an average consumption of 211 DDDs during the preceding six months. During the first 6 months, the difference in the proportion responders between the TS and the control group was 3.2% (95% CI 0.8;5.6). The adjusted relative risk of this outcome was 1.26 (95% CI 1.06;1.51). The comparison between the PV intervention and the control group during the 6-12 month period of the trial revealed no relevant differences (risk difference 0.4%, 95% CI -1.99;2.79); adjusted relative risk 0.99 (95% CI 0.84;1.22). The mean adjusted difference in DDD per patient in the TS - control group comparison was -3.0 (95% CI: -8.9;2.9) and in PV - control group comparison -5.82 (95% CI: -12.4;0.73).

Conclusion This health insurance company-initiated intervention aimed at optimising ASD prescription in primary care had a moderate effect on ASD consumption. In contrast to telephone assistance, practice support visits seemed not to reduce ASD prescription rates.

Introduction

Many studies demonstrated that only active, multi-faceted intervention methods are effective in implementing clinical practice guidelines. Based on the barriers that general practitioners (GPs) experience during implementation, tailored interventions are required in order to change routine clinical practice of GPs.[1, 2, 3, 4] Such programmes will be more successful when aimed at improving GPs' competence within their organisational and professional context by offering practical attributes and by avoiding complex steps.[5, 6, 7, 8, 9, 10, 11, 12]

An important focus of these programmes is the prescription of acid-suppressing drugs (ASDs) by GPs. ASD is a major burden of health expenditure in most western countries, with annually increasing volume and costs.[13] About 3.5% of the population is using ASD on a continuous day-to-day basis but the indication is often questionable.[14, 15, 16, 17] According to present clinical practice guidelines 'on demand' or 'intermittent' drug consumption are the regimes of first choice for most of the patients with dyspeptic or reflux symptoms.[18, 19, 20] ASD consumption proves difficult to change, because of both the high effectiveness of ASD on acid-related symptoms and the prompt acid rebound effect that patients experience after cessation.[21, 22, 23, 24, 25] Efforts to change ASD prescription practice of physicians have so far not been very successful. Simple distribution of clinical practice guidelines, patient information or stop protocols did not prove to be effective in changing GP prescription policy in earlier studies.[26, 27, 28, 29, 30] The impact of financial incentives on the effectiveness of such programmes remains uncertain.[31, 32, 33, 34, 35, 36, 37, 38]

In 2004 Agis, the major Health Insurance Company (HIC) in the central region of the Netherlands launched a multi-faceted intervention programme to optimise ASD prescriptions. The programme was based on the Dutch dyspepsia guideline and consisted of a 'stop protocol' and included a list of chronic ASD users per practice. In an earlier study we reported the lack of effectiveness of relatives "passive" interventions, such as the simple distribution of clinical practice guidelines, and of the provision of financial incentives.[39]

In this study we evaluate the effectiveness of two active interventions, telephone support and practice facilitator visits, in the implementation of this managed care programme.

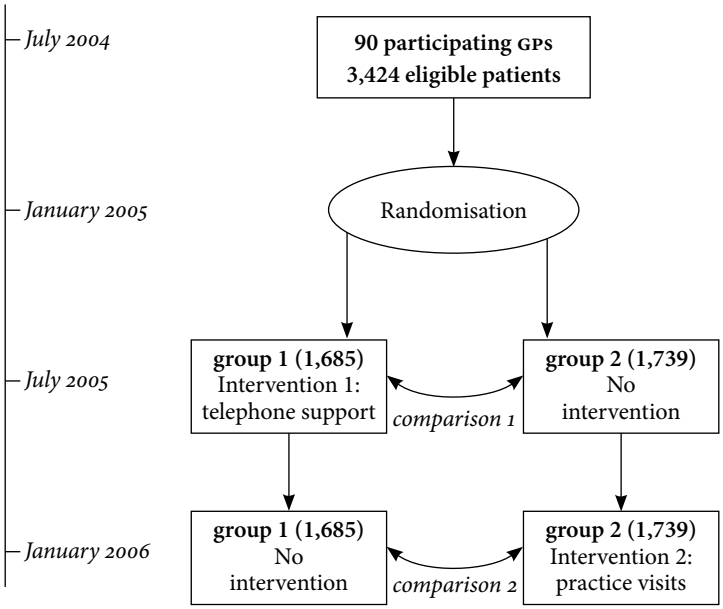
Methods

Study design and setting We conducted a sequential cluster randomised controlled trial in primary care in the central region of the Netherlands, where the Agis health insurance company covers healthcare provisions for over 1.5 million inhabitants. All regional GPs with at least each 250 patients ensured with Agis (n=434), were invited to join the ASD managed care programme.

We evaluated two interventions (repeated telephone support (TS) and practice visits (PV)) in a sequential design. Participating GPs were randomly allocated to one of the two groups. The GPs allocated to the TS group received repeated telephone support and a 'stop protocol' during the first 6 months, but no intervention during the 6-12 month period (when they served as the control group for the practice visit (PV) intervention). Those allocated to the PV group received no intervention during the first 6 month period (during which they served as the control group for the TS intervention), but received practice visits and a 'stop protocol' during the 6-12 month period.← *figure 1*

Interventions All GPs received a so called 'stop protocol', consisting of instructions for rational long-term ASD prescriptions according to current professional guidelines, examples of strategies for (gradual) termination of ASD use, a list of patients on long-term ASD per practice and patient information letters about rational ASD use in different languages. Further implementation of this 'stop protocol' was left to the GP. As compensation for the additional work during the intervention, GPs were granted three extra consultations (in total € 75.-) per included patient. Every three months, the GPs received an updated list of the patients in their

FIGURE 1 **Flowchart intervention study**



practice using ASD, as well as those who reduced their ASD medication.

Intervention 1: telephone support GPs in intervention group 1 (TS group) only received an intervention during the first 6 months of the trial. They first received the 'stop protocol' by mail. In addition, they were contacted by phone by the practice facilitators, who explained the details of the intervention and answered questions. Three months later they phoned again to monitor and evaluate the implementation of the 'stop protocol'.

Intervention 2: practice visits GPs in intervention group 2 (PV group) only received an intervention during the 6 to 12 month post-randomisation period. Then, they were visited by practice facilitators (PV group) who introduced the 'stop protocol' personally and offered practical support to identify eligible patients. This practice visit was repeated three

months later to discuss problems with the implementation of the programme.

Control groups To assess the effect of the telephone support (plus stop protocol) ASD prescription parameters in the TS group and in the PV group were compared in the 6 month period following randomisation, during which the PV group received no intervention. To determine the effect of the practice visits (including the stop protocol) ASD prescription data in the PV group were compared with those in the TS group during the 6 to 12 month period following randomisation, when the latter group received no intervention.←

figure 1

Measurements Patients and GP characteristics and detailed prescription data were extracted from the Agis Health Database (AHD), which provides computerised lists of all delivered prescriptions. The AHD is updated every month and includes the name and demographic characteristics of each patient, the ATC-code, dose, amount and price of drugs, prescribing GP, and delivering pharmacist. Chronic ASD use was defined as the use of more than 180 defined daily doses (DDD) of ASD (H2RA and PPI) in the preceding year. Patients with co-medication of more than 30 DDD of NSAIDs were excluded, because of possible need for gastro-protection.

The volume of ASD was defined as the mean number of DDD per patient in the participating practices. Subsequently the costs of ASD were defined as the cost for the mean number of DDD delivered per patient. Costs were fixed on the drug price level at the start of the program. Baseline prescriptions, defined as the average number of DDD per prescription per GP, were categorised as up to 90, to 180 or more DDDs of ASD. Patients from non-Dutch origin (Moroccan and Turkish) were analysed separately. According to their insurance status, patients were categorised as employees, work-disabled, unemployed and those that utilised social insurance. Based on the

number of houses per square mile, urbanisation was defined as urban (high), suburban (mean) and rural (low).

Outcome The primary outcome parameter was the proportion of patients that substantially reduced their ASD use during the intervention period (i.e. the proportion responders). This was defined as a reduction in DDDs of at least 50% compared to the average number of DDD the patient used in the six months before the intervention. Secondary outcome parameters included the change in the mean number of DDDs per patient and the total cost of ASD prescriptions during the study period.

Analysis Chi-square tests were used to compare characteristics of GPs and patients between the comparison groups. Prescription values that were missing because of transfer to other practices were considered to have occurred non-randomly and were imputed by single imputation techniques. To assess the effects of the interventions studied a multilevel Poisson regression model was used; relative risks (RR) for the outcome "responder" with 95% confidence intervals were calculated. The effects of the intervention on the number of DDDs of ASD prescribed and on the costs related to these prescriptions were assessed applying multilevel linear regression analyses, reporting the regression coefficient of the differences in changes between the two comparison groups. Then, a multilevel analysis was applied, with patients per practice at the first level and GPs per peer group at the second level. First, a univariate model with the mean DDDs per prescription at baseline was constructed, followed by a full model with other fixed effect variables that included gender, age, ethnicity, insurance groups and urbanisation level of the patients as well as gender, age and the size of practice population of the GPs. Relative risk (RR) and regression coefficients (β) were both reported with 95% confidence intervals (95% CI).

Results

Baseline characteristics Of the 434 GPs in the region 90 (21%) participated in the programme. They were randomised to the TS group (47 GPs) and the PV group (43 GPs). The GPs in the two groups did not differ in mean age, in urbanisation of their practice or in mean number of ASD prescriptions. ← *table 1*

TABLE 1

Characteristics of participating GPs as well as practices and characteristics of patients using ASD (>180 DDD) in the intervention and control group (%)

		Intervention	Control	p-value
GP practices:		**n=47**	**n=43**	
Age GP				0.73
	-45	30	23	
	45-55	42	51	
	55+	27	26	
Urbanisation Practice				0.35
	Low	37	35	
	Mean	40	29	
	High	23	37	
Mean DDD per prescription				0.64
	<90	79	80	
	90-180	20	19	
	>180	1	1	
Patients:	**> 180 DDD**	**n=1685**	**n=1739**	
Gender				0.69
	Men	42	42	
	Women	58	58	
Age				0.48
	-44	16	15	
	45-64	40	41	
	65-80	33	34	
	80+	11	10	
Social status				0.22
	Work disabled	19	20	
	Employees	26	25	
	Social insurance	9	8	
	Unemployed	46	47	
Ethnicity				0.42
	Moroccan	3	3	
	Turkish	5	4	
	Others	92	93	

The number of chronic ASD users identified in the TS and PV group was 1685 and 1739 patients, or 37 and 41 per 1000 patients, respectively. The patients in both groups did not differ in gender, age or social status. Together, they were prescribed on average 214 (TS group) and 208 (PV group) DDD per patient in the 6-month pre-randomisation period. During the first 6 month post-randomisation period no patients were lost to follow-up. During the 6 to 12 month period 15% of the TS group and 8% of the PV group patients were lost to follow-up due to transfer to another practice.

Effects of telephone support In total, 285 (16.9%) of the chronic ASD users in the TS group responded during the 6 month follow-up period, compared with 239 (13.7%) in the control group (rate difference 3.2%, 95% CI 0.8;5.6; the RR was 1.24, 95% CI 1.02;1.50).← *table 2* Adjustment for peer group clustering and other variables in the multilevel analysis yielded a RR of 1.26 (95% CI 1.06;1.51).

In the TS group, the ASD volume dropped from 214.4 DDDs in the six months before to 200.5 DDDs per patient in the 6 month intervention.← *table 2* In the control group, the volume dropped from 208.0 to 201.2 DDDs during the same period. The difference between the changes in the intervention group (13.9 DDD) and the control group (6.8 DDD) was 7.1 DDDs per patient. Adjustment for peer group clustering, the prescription rate at baseline, and other fixed patient and GP characteristics, yielded a statistically non-significant DDD difference of β=-3.01 (95% CI -8.9;2.9) per six months,← *table 2* corresponding to an average annual reduction in ASD of 6 DDDs per patient. Savings due to ASD consumption reduction were 12.4 Euros (from 172.3 to 159.9) per patient in the intervention group and 9 Euros (from 167.2 to 158.2) per patient in the control group.← *table 2* The adjusted difference was slightly larger (β =-4.10, 95% CI -4.1;1.0).

Effects of practice visits In the second comparison, 263 (15.1%) of the chronic users in the PV group responded, compared to 248 (14.7%) in the control group (rate

TABLE 2

Proportion of responders, mean volume (DDD) and costs (€) of ASD prescriptions per patient (p/p) before and after the intervention, as well as differences between the intervention (TS) and control group (95% CI).
Relative risk (RR) of responders and regression coefficient (β) of difference in mean volume (DDD) and mean costs (€) of ASD prescription per patient (p/p), between intervention (TS) and control group, after adjustment from multivariate multilevel regression analyses. Poisson model for RR and linear model for β with 95% CI

6 Months period (1 phase TS)	Responders (<50% DDD)	DDD p/p Pre-intervention	DDD p/p Intervention	Costs p/p Pre-intervention	Costs p/p Intervention
Telephone support group (n=1,685)	16.9% (285)	214.4	200.5	172.3	159.9
Control group (n=1,739)	13.7% (239)	208.0	201.2	167.2	158.2
Difference (95%CI)	3.2% (0.8 ; 5.6)	6.4 (6.1 ; 6.7)	- 0.7 (-1.0 ; -0.4)	5.1 (4.8 ; 5.4)	1.7 (1.4 ; 2.0)
Crude RR and β (95%CI)	*RR = 1.24 (1.02 ; 1.50)*	*β = -1.46 (-10.8 ; 7.9)*		*β = -2.17 (-16.6 ; 11.9)*	
Adjusted RR and β (95%CI)	*RR = 1.26 (1.06 ; 1.51)*	*β = -3.01 (-8.9 ; 2.9)*		*β = -4.10 (-9.1 ; 1.0)*	

Multilevel analyses was performed as follows: 1) Multivariate simple analyses, adjusted for peer group clustering, 2) Multivariate baseline, adjusted for peer group clustering and mean difference of DDDof GPs in pre-intervention period, 3) Multivariate full model, adjusted for peer group clustering, DDD at baseline and case-mix, including sex, age, urbanisation, ethnicity, social status of patient and sex, age, number of patients of GP. (Full model for costs fitted by excluding urbanisation from case mix.)

table 3 difference 0.4%, 95% CI -1.99;2.79; the RR was 0.97, 95% CI 0.82;1.16). ← The adjusted RR was 0.99 (95% CI 0.84;1.22).

The prescription volume in the PV group dropped from 201.2 to 195.2 DDDs per patient compared to 200.5 to 200.7 DDDs in the *table 3* control group during the 6 month follow-up period.← The (crude) difference between the change in the PV group and the control

TABLE 3

Proportion of responders, mean volume (DDD) and costs (€) of ASD prescriptions per patient (p/p) before and after the intervention, as well as differences between intervention (PV) and control group (95% CI).
Relative risk (RR) of responders and regression coefficient (β) of difference in mean volume (DDD) and mean costs (€) of ASD prescription per patient (p/p), between intervention (PV) and control group, after adjustment from multivariate multilevel regression analyses. Poisson model for RR and linear model for β with 95% CI.

6 Months period (2 phase PV)	Responders (<50% DDD)	DDD p/p Pre-intervention	DDD p/p Intervention	Costs p/p Pre-intervention	Costs p/p Intervention
Practice visit group (n=1,739)	15.1% (263)	201.2	195.2	158.2	154.8
Control group (n=1,685)	14.7% (248)	200.5	200.7	159.9	159.4
Difference (95%CI)	0.4% (-1.99;2.79)	0.7 (0.4;1.0)	-5.5 (-5.8;-5.2)	-1.7 (-2.0;-1.4)	-4.6 (-4.9;-4.3)
Crude RR and β (95%CI)	*RR = 0.97 (0.82 ; 1.16)*	*β = -5.12 (-14.5 ; 4.2)*		*β = -1.85 (-16.0 ; 12.3)*	
Adjusted RR and β (95%CI)	*RR = 0.99 (0.84 ; 1.22)*	*β = -5.82 (-12.4 ; 0.7)*		*β = -3.96 (-9.6 ; 1.7)*	

Multilevel analyses was performed as follows: 1) Multivariate simple analyses, adjusted for peer group clustering, 2) Multivariate baseline, adjusted for peer group clustering and mean difference of DDD of GPs in pre-intervention period, 3) Multivariate full model, adjusted for peer group clustering, DDD at baseline and case-mix, including sex, age, urbanisation, ethnicity, social status of patient and sex, age, number of patients of GP.(Full model for costs fitted by excluding urbanisation from case mix)

table 3

group was 6.2 DDDs per patient. This difference became somewhat smaller after adjustment in the full multilevel model (β=-5.82, 95% CI: -12.4;0.73).←

The savings were 3.4 Euros (from 158.2 to 154.8 Euro) per patient in the PV group and 0.4 Euros (from 159.9 to 159.4 Euros) in the

table 3 control group;← the adjusted difference after 6 months follow-up was approximately 4 Euros per patient (β -3.96, 95% CI: -9.6; 1.7).

Discussion

We previously reported that passive introduction of a managed care program among GPs did not result in a change in ASD prescription *39* behaviour.← In this study, we demonstrated that additional active interventions to support the implementation of the programme do reduce ASD prescription rates, although the effects are modest. Patients have a 25% higher probability (adjusted RR; 1.26 95% CI 1.06;1.51) of reducing their ASD use by 50% or more ("responder") when GPs receive telephone support (plus a stop protocol). The effect on the total volume of ASD was modest: ASD prescription dropped only 3 DDD per patient over a 6-month period. Practice visits (plus a stop protocol) did not result in an increase in the number of responders (adjusted RR 0.99; 95% CI 0.84;1.22), while the mean, non-statistically significant reduction in DDD per patient was 6 DDD.

Comparison with other studies The proportion of patients in our study that successfully stopped was modest compared with an earlier study using intensive support *34* of both GPs as well as patients, where the success rate was 15%.← Our result do match those of other studies using audit and feedback *40* studies.←

Despite the fact that the intensive personal support of GPs and practice visits are generally considered effective in changing prescription behaviour, we could not demonstrate convincing clinical and economic results after implementing such a strategy. To overcome barriers as perceived by GPs in changing clinical practice, active support by a health insurance company (HIC) may not be the best strategy. One of the barriers will certainly be the time investment and the motivation required to persuade patients to reduce their ASD refills. It may well be that the prescribing GPs did not consider chronic ASD use as a problem, given the high patients

satisfaction and the perceived effectiveness and lack of side effects of the drugs. This may have hampered their motivation to convince their patients to reduce ASD intake. This is further complicated by the lack of time to discuss this during routine consultations, which
3 decreases their chances to successfully change medication use.←

Strengths and weaknesses This study was one of the first to evaluate a large scale health insurance
35 company-initiated intervention program in a RCT design.← The participating GPs were recruited from a large region, which contributed to the representativeness of the outcomes. Furthermore, we used the complete and accurate prescription dataset of the regional health insurance company to evaluate the effects of the intervention in the programme.

The small proportion of patients that actually reduced ASD could partly be attributable to the public discussion about ASD being a lifestyle drug that was ongoing during our study, urging the government to revise prices and the refunding policy of ASDs. As a consequence, ASD prescriptions could have dropped independently of the intervention program. In addition this public debate may have affected the motivation of the participating GPs in the intervention group and may have made GPs in the control group aware of the societal importance of limiting the ASD prescription.

A second reason for the limited effects observed in our study may be the fact that we left the inclusion of patients completely to the GPs. Essentially all chronic ASD users were eligible for participation in the study (with exception of chronic NSAID users) but the selection of patients depended entirely on the clinical judgement of the GPs. Although the participating GPs volunteered to participate, we had no insight into their motivation and GPs may have systematically excluded those chronic ASD users for whom they considered it too difficult to change their drug regime. This may explain the fact that GPs have selected an unexpectedly low number of patients, possibly with an understandable tendency to select those that required less support to cease ASD. Approaching eligible patients

directly by the research group might have resulted in higher numbers of patients willing to reduce ASD use and thus increased the beneficial effects.

Prolonged follow-up In our study the effect of active repeated telephone support seemed larger than that of practice visits. It should be emphasised, however, that the comparison between the practice visit intervention and the control group (which was the group not receiving any intervention during the intervention period, but receiving the telephone support during the 6 preceding months) may be somewhat problematic. Possibly, the benefit of the telephone support during these preceding 6 months may have exerted an extended beneficial effect during the 6 to 12 month period, thus artificially increasing the benefit observed in the control group and diluting the reduction in ASD prescription caused by the practice visits. On the other hand, at 6 months post-randomisation, the prescription rates in the PV group and the control group (i.e. those having received telephone support) were comparable. Alternatively, the effect observed in the practice visit intervention group may have been limited because the practice visits did not always take place during the first weeks of the intervention period. Consequently, in some practices the time left during the 6 month follow-up period after the interventions were introduced by the facilitator was too short to achieve an effect on ASD prescription rates. This is illustrated by the larger effect observed when the follow-up period was extended to 12 months in the PV and control groups: difference in DDDs per patient 10.4; 95% CI 3.8;16.9 (data not shown).

Conclusion We conclude that an active health insurance company-initiated intervention including repeated telephone support and a stop protocol in chronic users of ASD in primary care has a moderate effect on ASD consumption. In contrast to repeated telephone support, practice support visits do not seem to reduce ASD prescription rates. For optimal implementation of ASD

prescription programmes in primary care both the prescribing GP and the patient need to be motivated. To achieve this, additional interventions have to be considered, such as a patient support programmes through pharmacies or nurse practitioners.

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SUBMITTED AS:

The use of routine health insurance data for scientific research: potential and limitations of the AGIS HEALTH DATABASE

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9 The use of routine health insurance data for scientific research: potential and limitations of the AGIS HEALTH DATABASE

Abstract

Observational studies performed within routine health care databases have the advantage of their large seize and, when the aim to assess the effect of interventions, can offer a completion to randomised controlled trials with usually small samples from experimental situations. Institutional Health Insurance Databases (HIDs) are attractive for research because of their large size, their longitudinal perspective and their practice-based information. As they are based one financial reimbursement the information is generally reliable. Whether the HIDs' data sets meet de specific requirements to conduct several types of clinical studies is discussed according to the classification of the four different types of clinical research; i.e. diagnostic, etiologic, prognostic and intervention research. Next, the database of one of the major insurance companies in the Netherlands, the Agis Health Database (AHD), is described in detail. Finally the potential of the AHD for various types of research is illustrated using examples of studies recently conducted in the AHD. We conclude that HIDs such as the AHD offer large potential for several types of clinical research, in particular etiologic and intervention studies, but that at present the lack of detailed clinical information is an important limitation.

Introduction

Today, almost all institutional records are stored electronically. Access to such 'routine data' has greatly expanded the potential for epidemiological research. Due to their size and content these databases allow observational studies that may offer a completion to other study designs.[1, 2, 3] For example, randomised controlled trials (RCTs), the gold standard in intervention research, are usually performed with 'designed data' of specific clinical information, collected in an experimental situation of a limited and highly selected patient sample. Databases from healthcare, insurance or governmental institutions generally have a large size and are composed of routine care data from 'practice-based' registrations, independent of research infrastructures and can be accessed efficiently. The potential of such studies was illustrated even before the automation era by a study of the mortality of workers with asbestos exposure in 1935.[4] More recently, they have proven to offer excellent opportunities to study effects of interventions and, in particular, side effects of drugs.[5, 6]

Health Insurance Databases (HIDS) such as those of the Health Insurances Companies in the Netherlands, Krankenkasse in Germany and Medicaid in the USA have a high reliability due to their background of financial reimbursement of healthcare deliverables to care providers. A disadvantage is that they usually lack clinical information and contain only demographic patient data. The absence of detailed information on specific risk factors or on confounding variables limits detailed studies of causal relationships. On the other hand, various types of observational studies such as studies on drug utilisation, disease course or effects of (drug) treatments are feasible in HIDS. For many of these studies the long follow-up time of HIDS creates extra benefits.[7, 8, 9] Development of Health Maintenance Organisations (HMOS) such as Kaiser Permanente in the USA has enhanced the potential of HIDS' research, mainly because HMO databases merge clinical and insurance data

from the same organisation thus facilitating the linkage to clinical information.[10]

The potential of HIDs for research depends on the type of information that is registered. The latter varies considerably between insurance companies.[table 1] Although HIDs usually contain a lot of patient-linked data, the validity of the data for research has hardly been studied. It seems that accuracy and representativeness are generally high but the practical applicability of HID data for different types of research critically depends on the type and the quality of the stored data.[11, 12]

TABLE 1

Examples of health insurance databases (HID) and a health maintenance organisation (HMO)

Database	Type	Data stored	Research example
Agis Health Insurances [7]	HID (the Netherlands)	GP consultations, drug prescriptions, surgical procedures, referrals, outpatient services, hospitalisation, dates, diagnostic treatment protocols	Upper respiratory infections and antibiotics
Northrhine-Westfalia Ortskrankenkasse [13]	HID (Federal Republic of Germany)	Diagnoses, drug prescriptions, surgical procedures, outpatient services, hospitalisation	Myocardial infarction and social classes
Medicaid [14, 15]	HID (USA)	Diagnoses, drug prescriptions, surgical procedures, outpatient services, hospitalisation, dates	Breast cancer and mortality
Kaiser Permanente [16]	HMO (USA)	Diagnoses, drug prescriptions, surgical procedures, lab results, outpatient services, hospitalisation, dates	Hypertension treatment and high blood pressure

In this article we discuss the potential of HID for various types of scientific research and the specific requirements of the data set, We illustrate this with the database of Agis, one of the larger health insurance companies in the Netherlands and demonstrate the

potential of the Agis Health Database (AHD) for research with various studies that were conducted with the AHD.

Types of clinical research

Although health insurance databases can be used for many research questions, their application depends on the typically required variables for each type of research and the validity of its information.[1, 9, 17] In clinical epidemiological practice, the following types of research design can be distinguished.[18]

Etiologic studies In etiological research, causal relationship between a determinant (i.e. risk factor) and a disease (or outcome) is assessed. Obviously, adequate information on the causal determinant and on the disease of interest is essential. Since the aim of an etiologic study is to determine causality, detailed information on potential confounders that may distort the association between the determinant and the outcome is crucial.[19] Such confounders are variables that both increase the risk of the outcome and are related to the causal factor studied. Typical examples include age, gender, lifestyle parameters, socio-economic status and co-morbidity. As detailed information on such data (apart from age and sex) is not always contained in HIDS, proxy indicators can be used; for example anti-diabetic drugs for the diagnosis of diabetes. Alternatively, information about additional potential confounders such as socio-economic class, income and ethnicity can be obtained through linkage with other databases. With these methods the available data in HIDS make etiologic studies feasible, but some confounders may still be absent or not adequately measured. This will limit the potential to address etiologic research questions.

Intervention studies Intervention studies aim to prove that an intervention (such as drugs or other medical treatments, but also health care interventions such as a new guideline or a managed care programme) improves the prognosis of patients and that this intervention is causally related to the prognos-

tic benefit. Randomized controlled trials (RCTs) are the gold standard in this type of research, because the tools typical for RCTs, most notably randomization, but also blinding and placebo/sham treatment, ensure comparability of the intervention and control group of the trial. Because HIDs are observational by definition, allocation to treatments is based on daily practice and thus everything but random. HIDs can however be useful in the conduct of RCTs, when the trial is performed within the region of the insurance company involved and the information in the database can be applied to measure the outcome. An example is an RCT that assessed the effect of an intervention strategy aimed at reducing antibiotic prescription rates. In this study the intervention strategy was randomly allocated to half of the primary care practices in the study region.[7] Observational studies, for example cohort or case-control studies, are an alternative for RCTs in the assessment of the effect of interventions. Particularly, when the follow-up period is long or unknown and in case the outcome is relatively rare, HIDs offer good opportunities. Another major advantage of HIDs in observational studies is the inclusion of "real" patients, i.e. those patients (with co-morbidity, co-medication) that actually receive the intervention in daily practice. To determine the effect on the relevant outcome caused by the intervention in a valid way, the HID must include detailed information about the intervention (for example drug treatment), about the outcome and about potential confounders. As in etiologic research, the lack of detailed information on potential confounders may seriously hamper the validity of observational studies assessing causality.

Diagnostic studies Diagnostic studies usually aim at determining the value of a new diagnostic test (e.g. a novel blood test) in addition to easily available clinical information (typically results from history taking and physical examination) in confirming or ruling out a particular diagnosis in patients suspected of that disease. Alternatively, the objective of diagnostic research is to derive the optimal diagnostic strategy, including a limited set of

diagnostic items from history taking and physical examination and more complicated tests in suspected patients. For several reasons HIDs are not suited for diagnostic research. First, the domain of diagnostic studies, i.e. patient suspected of a particular disease, is impossible to identify in HIDs. Second, signs and symptoms are usually not included in such databases and although HIDs often do contain information on whether a specific laboratory or other diagnostic test was performed the result of the test is usually not stored. Finally, the validity of the outcome (in diagnostic research the disease of interest) should be ensured. In most HIDs the registration of disease codes are not registered. Although the diagnosis can be approached using indicators such as prescriptions, such proxy indicators are usually not valid enough to approach the "gold standard" in diagnostic research.

Prognostic studies The objective of prognostic studies is to predict the course ("prognosis", e.g. the 1 or 5 year probability of complications or death) of patients with a particular disease, as a function of the individual values of multiple prognostic variables, such as age, sex, blood parameters or other indicators of disease severity. Importantly, the aim is *to predict* the future course of the disease and *not to explain* it. Consequently, causality is not involved here and confounding is not an issue, as is the case in diagnostic research. The domain of such studies is usually patients with a particular condition, but could also be patients undergoing a medical intervention or, simply a newborn.[20] The study is usually performed within a well-defined cohort of patients followed for an appropriate period of time. These designs require the presence of data that enable identification of the patient's condition and the potential prognostic determinants. As disease classification, such as ICD or ICPC coding systems, is usually not included in HIDs, proxy indicators have to be used. This and the fact that information on relevant prognostic determinants may be invalid or missing, altogether limit the use of HIDs for prognostic research questions.

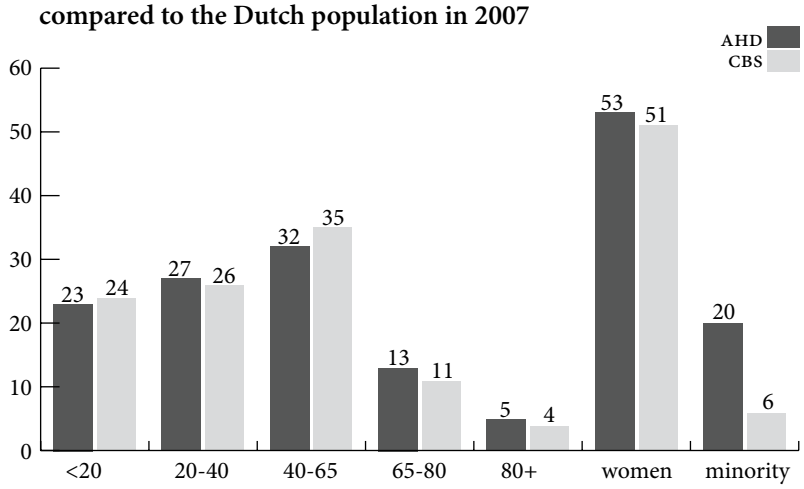
The Agis Health Database

Population Agis Health Insurance Company is the main health insurance company in the central part of the Netherlands. Until 2006, AGIS provided healthcare cover for more than 1.5 million residents. With the introduction of the new Health Insurance Act in 2006, under which health insurance companies were obliged to ensure all candidate clients and competition between companies increased, this number dropped with about 20% to 1.2 million. After the system change in 2006, the number of insured women decreased slightly by 2% (to 52.5%), the number of clients between 20-40 years decreased by 5% (to 26%) and the number of clients from ethnic minorities increased by 3% (to 20.5%). Although the AHD is not completely representative for the entire Dutch population, it does represent the urbanised area of the Netherlands (Statistics Netherlands 2007).←

figure 1 & 2

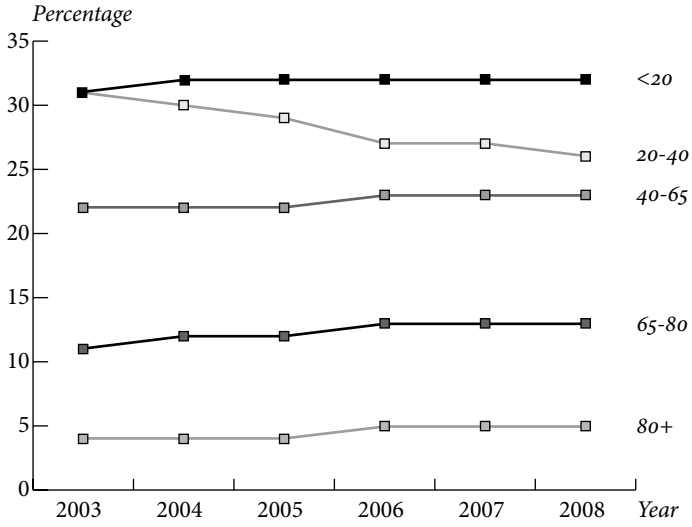
FIGURE 1

Gender, age and ethnic minorities* in the AHD compared to the Dutch population in 2007



* Minorities are only ethnic Moroccan, Turkish and Surinamese

FIGURE 2 **Trend figures of the AHD population by age, 2003-2008**



Data stored in the AHD The AHD records payments for the provision of all medical care to its insured patients. The database largely consists of three domains of information, i.e. that on 1) patients, 2) healthcare professionals and 3) health services provided. All three are linked to the patient's individual ID. The first two domains contain demographic data of patients and healthcare providers. The latter includes extensive records of all outpatient diagnostic and therapeutic provisions. It includes information on all drugs delivered by pharmacists, such as the type (ATC codes) and dosage of medication (defined and prescribed daily doses) , as well as on the prescriber, the date of delivery and the costs.← *table 2* Drugs delivered through hospital pharmacies and over-the-counter medication are not registered in the AHD. The database also includes most of the health services delivered by GPs and other primary care professionals, such as type and date of GP consultations and of chronic disease management programmes run by practice nurses in primary care. Also included is the background (specialism) and duration (days) of hospital admissions, as well as information about diagnostic and therapeutic services delivered in hospitals. Currently, the AHD does not include disease classification

codes, neither from primary nor from hospital care. Recently a system of diagnostic/treatment codes (In Dutch: DBC-codes) was introduced in the Netherlands for the reimbursement of hospital services. This system does require an appropriate diagnosis of each patient involved.

TABLE 2 **Data stored in the Agis Health Database**

	Patient data	HC provider data	Health service data
Coverage	1.2 million citizens throughout the country; 0.9 million in the middle region of the Netherlands	In dominant region : 2000 GPs 400 pharmacists 20 hospitals and specialists	All primary and secondary medical care services, e.g.: 12 million prescriptions 1 million specialist referrals 3 million physiotherapy sessions
Variables	Citizen administration number Age Gender Postal code (translated to social class category) Ethnicity Enlisted GP, Pharmacist	AGB number Age Gender Practice address Urbanisation grade	GP: Consultations, practice nurse services, referrals, consultation dates Pharmacist: ATC code, daily dose, price, prescriber, delivery dates Specialist: DBCcodes, length of hospitalisation period, type of care
Quality	High precision Representative	Continuous update of registration	Continuous update of registration
Limitations	Poor follow-up after transfer to other insurance company No death registry	Practices, and not individual GPs and specialists, are linked to services	No disease codes No over-the-counter and hospital prescriptions.

Validity The registration of pharmacy and other healthcare deliverables is complete and accurate, because of the economic function of the database. Health services are only reimbursed to the provider after extensive control of the electronic registration in a mandatory (national) format. This virtually excludes coding errors.[11, 21] The AHD has some limitations from a research perspective. The major restriction is that limited clinical data are contained. For example, the diagnosis of the patient is not

recorded, , neither is the indication for prescriptions nor the results of diagnostic tests.[22, 23] The follow-up of patients is sometimes incomplete due to a switch to another insurance company. Only outpatient prescriptions are reimbursed, so medication administered during hospitalisation is not recorded. Finally, the database contains only information about the delivery of drugs by the pharmacists, and not about the actual consumption by the patient (adherence), although there are methods to calculate adherence by combining dispensed drugs and subsequent prescriptions.[24]

Linkage To overcome the lack of clinical information, the AHD was linked to other databases such as those of of regional (e.g. hospital, psychiatric and primary care databases), or national (cancer databases, death registries) databases.[24] Currently, a virtual network (the so called Mondriaan project) is built in cooperation with several academic and non-academic institutions, that links several databases including the AHD on a structural basis. In the near future this network of permanently linked databases will be able to efficiently provide complex datasets for research purposes. To protect privacy during this linkage procedure a third trusted party is involved, that uses a so-called chance-linking process to identify patients on the basis of three individual characteristics: sex, age and postal code. In the newly merged data set the personal identification tag is removed before delivery to researchers to ensure the confidentiality of the information included in the database. This linkage procedure has greatly extended the potential of the AHD for research as it facilitates enriching the data set with the clinical information lacking in its original setup.

Privacy conditions of the AHD The AHD is subject to Dutch privacy laws. This allows the use for scientific research provided that results cannot be traced to individuals. A scientific committee assesses requests from researchers for datasets, and decides whether conditions for scientific and clinical relevance are met. Data sets are made available strictly

under the condition of anonymity and researchers are called to ensure that datasets are stored safely are not accessible to others. After use, the destruction of data is mandatory.

Examples of research conducted in the AHD

Intervention studies An example of a randomized trial performed within the framework of the AHD is a study assessing the effect of a multi-facetted intervention programme aimed at optimisation of acid-suppressing drugs (ASD) use in primary care. GP peer review groups (including on average 10 GPs) were randomly allocated to an intervention group subject to the managed care programme and a control group receiving no intervention ('usual care').← *table 3; 25* The primary outcome was the number of patients that successfully reduced ASD intake by more than 50%. Secondary outcomes were the changes in volume and costs of ASD prescription. Chronic ASD use was defined as more than 180 DDDs annually, which takes a prolonged exposure factor into account for intermittent or on-demand use.← *26, 27* Due to the dynamic character of the AHD population, some patients were lost to follow-up because they switched to another insurance company. Multilevel regression analysis was done to adjust for relevant patient and GP practice characteristics that differed between the two comparison groups and that were available in the AHD. There was no significant difference in the number of patients that reduced ASD consumption, nor in volume or costs of ASD prescription.

Etiologic studies Boelman et al conducted a study in the AHD to determine the causal relationship between the presence of chronic somatic diseases and the occurrence of psychiatric disease.← *table 3; 28* A cohort of patients with and without chronic somatic disease was selected by means of proxy indicators based on prescriptions for specific somatic disease, using ATC codes. Patients with or without chronic somatic diseases that received psychotropic medication (as a proxy for psychiatric disease) during a one year follow-up period were identified. Cox regression analysis was

performed to quantify the association between the presence of chronic somatic diseases and prescription of psychotropic medication, adjusted for potential confounders, such as age, gender, ethnicity and socio-economic status.[27] The results showed that 10% of the patients with chronic somatic diseases received psychotropic drugs , which was twice as much as in those without somatic disease.

Diagnostic and prognostic studies As explained earlier there are several reasons why it is virtually impossible to perform diagnostic research in health insurance databases. Prognostic studies may be possible, albeit that the lack of clinical information limits the application of these databases. In the AHD, cohorts of patients with specific conditions can be identified using proxy indicators such as the use of medication specifically targeted at the disease. A limited number of potential prognostic determinants are available in the database, such as age, sex, ethnicity, socio-economic status, current drug treatment and co-morbidity based on prescriptions.

Although no typical prognostic study, the study by Helsper et al illustrates the potential of AHD for this type of research.[29] In this prospective study authors aimed to predict the use of adequate gastro-protection with proton pump inhibitors (i.e. the outcome) in patients chronically using NSAID, as a function of risk factors, including age, peptic ulcer history and several types of co-morbidity relevant for gastric complications. A logistic regression model was used to identify independent predictors of adequate gastro-protection. All potential predictors were extracted from the AHD. Relevant co-morbidity was identified using specific prescriptions as a proxy indicator. The study demonstrated that 30% of the patients on NSAID at serious risk of gastric complications did not receive adequate gastroprotection, and that age, the use of corticosteroids and of SSRIs were independent predictors of adequate gastro-protection in patients on chronic NSAID medication.

Discussion and conclusion

Institutional databases such as the AHD offer excellent potential for observational research due to the size of the data set, the length of the follow-up and the accuracy of the data. In general, they are representative for the source population although regional population differences will be reflected in the data sets.

The main drawback of the institutional data for research purposes is the of lack clinical information such as reason for encounter, presenting complaints, coded diagnoses, complications and cause of death. In several studies performed in the AHD these limitations were, at least partly, overcome in two ways. First, many clinical outcomes can be approached by the use of proxy indicators such as drug prescription data (for diagnosis), referrals (for treatment) or diagnostic tests (for reason for encounter). These proxy indicators have intrinsic limitations due to, for example, overlapping indications, inter-physician variation in referrals and prescriptions and variations in individual prescription policies. Alternatively, clinical information can be added to the data set by linkage to other databases such as those from hospital or primary care registrations or to registries specifically monitoring e.g. causes of death, types of cancer, psychiatric diseases. Usually, linkage will not be possible for all individuals, but given the size of health insurance databases linkage to a more or less random subset of patients included in the database will neither bias the findings nor limit the statistical power of the studies.

By the nature of insurance data, the number of errors in the registration of variables in the AHD is usually limited. Some validity problems may, however, occur. Taking the example of studies on the effect of drug interventions, a type of study often conducted within health insurance databases, some of these problems will be discussed briefly. Limitations of the Agis Health Database for such studies may be caused by inadequate follow-up of cases, the use of proxy instead of true indicators of diseases, the non-inclusion of

OTC medication, problems to quantify drug adherence and to adequately adjust for confounding by indication.
To what extent these problems occur depends on the type of research question and several methods are available to overcome them. For example, missing data could be completed by imputation techniques. One of the major problems with the use of prescriptions as proxy indicators occurs when there are no specific prescriptions for the diseases under study. Prednisolone or betablockers, for example, can be prescribed for many indications. Then, additional selection methods, such as use of the combined diagnosis/treatment code (DBC) may be helpful. Also lack of information on OTC medication, and adherence to medication may pose problems in studies on drug effects. Since most drugs in the Netherlands are only dispensed based on prescriptions, the problem of missing OTC data is limited to those drugs, such as NSAIDS, aspirine, H2 blockers, laxatives, that are often sold over the counter. As mentioned before, drug adherence can be estimated by combining data on the actual prescriptions and subsequent dispensed data of the drug. When important confounders are missing in the database, however, the validity of studies on the effect of drug therapy (as in all studies assessing causality) is truly at stake. Then, only information on these confounders obtained from external data sources though linkage methods can prevent biased results.

Conclusion Health insurance databases, such as the AHD, include valid health care data from a very large population. This offers great potential for epidemiologic research. The main advantages of HIDS are, the large size of the database, the fact that they include routine 'daily practice' data, and the long term follow-up. Given the data included in the AHD the database seems most useful for etiologic and intervention research, albeit that the lack of adequate information on potential confounders may be an important limitation. Since earlier studies showed that the ADH data can be fairly easily linked to other databases, the enrichment of data by linkage could be instrumental in obtained crucial information on

relevant confounders and further extend the range of studies that are possible to conduct in AHD.

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10 General discussion

The Agis ASD reduction programme; conclusions

Agis launched a managed care project among general practitioners aiming at optimising ASD prescription in primary care. In a randomised design we evaluated the effectiveness of this programme, and of the various implementation strategies applied, including more passive approaches, such as sending lists with chronic ASD users to GPs and offering reimbursement for extra time spent to coach patients to reduce ASD intake and more active strategies, such as repeated telephone support or practice visits by practice facilitators. Based on this evaluation several conclusions can be drawn:
The overall effectiveness of the managed care programme was rather disappointing, both in terms of the number of patients that reduced ASD intake considerably (responders) as well as in the overall number of DDDs prescribed and in cost reductions achieved. Compared to the control group the number of responders was only four percent higher in practices of GPs receiving the more passive implementation strategy, and did not increase in the group allocated to practice visits from a facilitator. In contrast, the responder rate in GPs receiving repeated telephone support increased by 25%. The average ASD intake per patient decreased only marginally during both the more passive and active programmes, with one and six DDD per patient per year under the passive and the active implementation strategy respectively. Beforehand, it was expected that the programme would reduce unnecessary use of ASD in at least a quarter of the patients, and that extra costs of the programme (for management, consultation fees and practice facilitators) would be compensated by the savings on ASD prescriptions.[1, 2, 3] Despite the broad implementation of the programme, with financial compensation and practical tools to support participating GPs, these goals were not met. Various factors may have contributed to this, but we consider the fact that not all, or a considerable proportion of eligible patients were actively approached for participation of major importance.
Our second conclusion is that –despite the disappointing overall result– this evaluation once more confirms the present consensus

that for projects aiming at changing clinical practice active implementation strategies provide better results than passive ones.[4, 5] In practices of GPs who received practice support more patients responded, and both the number of DDDs prescribed and the costs for ASD prescription dropped more as compared to the control group. Finally we conclude that managed care projects, aiming at both cost control and quality improvement, are an accepted and potentially efficient way for health insurance companies to optimise the cost-effectiveness of prescription policies by medical professionals. The majority of the patients were prepared to participate in this ASD reduction programme, and most regional GPs were willing to participate in the programme.

The Agis ASD reduction programme; lessons to be learned

The programme's unique character In the past, many attempts have been made to rationalise GPs' prescription policy, but either professional or governmental organisations initiated most of them.[6] Given the evolving role of health insurance companies (HIC) in expenditure control and quality improvement in health care the Agis ASD reduction programme is an interesting and unique experiment.

Initially Agis planned the ASD "reduction" programme mainly for economic reasons, in an attempt to control the ever-increasing costs for dyspepsia treatment. Given the growing demand for improving quality of care the ambition of the programme changed into a prescription "optimalisation" project. The background philosophy was that improvement of ASD prescription would be less expensive in the long run. Thus, the Agis programme became a pilot project for gaining experience with health insurance company driven interventions aimed at optimising (ASD) prescriptions. The large scale at which the programme was implemented fuelled expectations that robust and generalisable results could be obtained.[7]

The second unique feature of the programme is the fact that it is the first time that a health insurance company programme has been

properly evaluated, using scientifically sound methodology, including tools such as a comparison group, random allocation and statistical techniques to adjust for clustering and for incomparability of patient and GP characteristics. Traditionally, changes in the health care system are usually directed by presumed benefit, and not by proven effectiveness of the interventions at interest.

Strength and weakness Although both the programme as well as the scientific evaluation were designed in accordance with current scientific standards and clinical knowledge we met some serious constraints.

The fact that we left the inclusion of the patients completely to the GP may have been attractive because of its pragmatic approach; it is likely to have reduced the potential beneficial effects of the programmes. The GPs' motives for actively approaching individual patients remained unclear. This may have resulted in a highly selective subgroup of eligible patients being offered support to reduce ASD intake – depending on, for example, the motivation of these patients, alleged chance of success and the perceived efforts required to bring about a change in ASD use.

In addition, the public discussion during the programme about ASD being costly "lifestyle" drugs, may have caused a decrease (or reduces increase) of ASD prescriptions in both the intervention and control group, further diluting the observed effects.

Finally we chose to enrol the programme at a large scale, region wide, to get a realistic impression of the reception of such HIC-initiated programmes in primary care practice. The fact that we chose not to approach each GP individually for participation made it difficult to estimate how many GPs did not comply because they disapproved of this initiative of the insurance company or because they considered interventions in chronic, in general satisfied, ASD users not a priority.

Implications of the results Although the overall results were modest, the programme has yielded

some interesting tools that can be used for future programmes. In the project, Agis demonstrated that it is capable to adequately distribute both, generic information such as a stop protocol and dyspepsia guidelines, as well as individualised information such as a list of patients eligible for the project; the latter based on its database structure. The infrastructure of health insurance companies seems equipped to manage this complex logistical process.
The work of the practice facilitators was appreciated by the GPs. The facilitators adequately managed to offer in-practice support to all participating GPs in a relatively short time period, at the same time taking an individualised approach.
Insurance data, such as in the Agis Health Database (AHD), is a very adequate source to identify and monitor patients on ASD prescription. The AHD proved to be very useful to identify chronic users, measure outcomes and to analyse the overall effectiveness of the programme.
In the programme we choose not to invite the eligible patients to participate, but to leave this to the prescribing GP. As explained above, this could be one of the reasons of the modest effects of the current programmes. In future initiatives a patient oriented approach could be taken, using different routes for recruitment, such as through mass media or personal invitations.

Health Insurance Companies and quality improvement

New responsibilities During the time of the Sick Fund Act the national health care budget was determined by politicians and the task of the Sick Funds was to control the financial compensations. To a certain extent they could develop initiatives to limit the growth of the budget, but as far as the pharmacy costs were concerned these initiatives were never very successful.[8] In the new, market oriented, health care system the tasks of the companies changes considerably. In the interest of their clients and within the limits of the national budget they themselves had to redefine the relation between price, quality and premium.

Costs exceeding their budget became a company risk and not a public risk, and the insurance companies had to start thinking in macro-economic models. In the light of this new strategy they nowadays contract health care professionals and negotiate about volume and price to ensure the most cost-effective health service provisions.[9] This includes a continuous search for innovations, both in clinical services as well as in health care management.

Quality of Care The insurance company and the health care professional meet in their mutual search for quality of care. In addition they have a shared interest in increasing their patients'/clients' satisfaction. The professional intends to provide excellent clinical care on the micro-level of his or her surgery or practice; the insurance company aims to contract high quality care for its clients on the meso-level of the professional. However, the professional often lacks the time, the instruments and perhaps also the objectivity to review the quality of care he or she provides. The HIC has access to instruments to assess the quality of care delivered by professionals, both on a micro and a meso-level, although the validity of many quality indicators remains controversial. All information regarding health care provisions are stored in the HIC databases, which, if properly analysed and interpreted, may offer effective instruments to monitor quality of care. Provided that the insurance company gains the professionals' trust regarding the objectivity of this quality assessment, there is an excellent opportunity for quality of care improvement.

Optimising clinical practice; the role of the Health Insurance Company

Insurance companies and health professionals should cooperate in managed care programmes to optimise clinical practice. The need for quality improvement is of common interest and the managed care intervention should, in principle, originate from the currently available clinical guideline developed by the health care professionals (in the studies in this thesis the GPs) themselves. Further

development of active multiple faceted implementation strategies is important for successful programmes in the future. In such an active approach individual health care professionals need to be convinced that quality improvement requires extra efforts in daily practice. In addition, individual support and in practice tools are essential for successful implementation. These instruments should be easily and instantly accessible. An adequate distribution of a protocol, lists of eligible patients and patient information brochures are time saving for the GP. During the implementation of the programme the GP needs to be informed about his or her success rate in comparison to colleagues (bench mark) and should receive feedback on the final results of the project. Finally patients' involvement is an equally critical condition for success of programmes aiming at changing clinical practice.

Improving the strategy The best strategy for implementation of a HIC-initiated managed care project consists of the following elements: close cooperation with professionals, individual and instrumental support, patient involvement and adequate monitoring of participation. The managed care project should be designed in close collaboration with professionals. Indicators of performance need to be available to monitor the progress of the project and to measure outcome. The database of the insurance company can provide individual feedback of indicators of performance thus stimulating quality improvement programmes. Finally patients have to be informed about the benefits of the programme and should be stimulated to participate.

Critical conditions for success Successful programmes aiming at improving quality of care require a good relationship with the professionals and their organisations. This is not an automatic development, building relations requires long term investment.
In this context the present HICs policy of preferred providers is a first step to intensify the relations with professionals, which may

lead to a structural cooperation in innovative managed care projects.

Optimal support of individual professionals participating in programmes and adequate communication of the results is important for the success of managed care projects. This requires a professional field team of HIC employees to maintain the relationship with individual health care professionals. The appointment of practice facilitators by HICs seems an attractive development, but the future field team needs to be extended with expertise on medical issues, data interpretation and technical support.

Insurance companies have to expand their informatics departments in order to be able to further develop the instrumental role of their databases in managed care projects. For effective use of these databases tailored programmes to extract and analyse data and standard operating procedures (SOPs) have to developed and possibly adapted for specific projects.

Towards a broader implementation of managed care programmes

The Agis ASD reduction programme focussed on the prescription domain, but the experiences gained are equally applicable in other clinical domains, both in primary and in secondary care. In recently developed managed care programme's such as Diagis (in diabetes) and in COPD patients some of the lessons, like the important role of practice support, performance indicators and adequate data collection have already been incorporated. Although transmural care projects on cardiovascular risk management and heart failure have recently started, secondary care is still a relatively unexplored domain for HIC initiated managed care projects. Ongoing improvement of quality of care requires a joint investment of patients, health care professionals and insurance companies.

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English summary

The use of Acid suppressing drugs (ASDs) In the Netherlands increases more than 10% annually. Of the Dutch population 3.5% uses ASD, in 90% of the cases proton pump inhibitors (PPIs), on a daily basis. However, indications for long term use of PPIs for gastrointestinal complaints are often not evidence based and many patients might be able to stop or to switch to a symptom-guided, so called 'on-demand' use.

In today's more market oriented health care insurance companies have a major role in maintaining the correct balance between costs and quality of care. Within health care expenditure pharmacotherapy, which is responsible for 25% of the national health care budget, has always been a major focus. Insurance companies can increase cost-effectiveness of drug prescription by the implementation of managed care programmes. Within this context Agis, one of the leading Health Insurance companies in the Netherlands, has initiated a programme to optimise ASD prescription in its region. In order to identify the optimal implementation method the programme was introduced using different strategies.

In this thesis we report the scientific evaluation of this Agis ASD reduction programme, and evaluate its effect on volume and costs of ASD prescription. In the first two pre-studies reported in this thesis (Chapter 2 and 3) we analysed the prevalence and the indications of ASD consumption in the Netherlands. We reviewed the international literature to assess the best implementation strategy for the programme (Chapter 4). Next we tested the managed care programme in a pilot study among GPs (Chapter 5) and evaluated the experiences of patients with the programme (Chapter 6). In a randomised clinical trial we evaluated the effectiveness of the programme in the Agis wide region, using different implementation strategies (Chapter 7 and 8). Most evaluation was done with data from the Agis Health Database (AHD), and in the final chapter we evaluated the possibilities of this AHD for scientific research in a broader perspective (Chapter 9).

In **Chapter 2** the increased use of pharmaco-therapy for dyspeptic complaints was analysed over three successive years using data from the AHD. The association between the increased ASD use and patient or physician related variables were investigated in a cohort of almost half a million people insured with Agis. The annual increase in PPI prescription of 6-10% appeared to be correlated to gender and age (mainly elderly women) and with the use of non-steroidal anti-inflammatory drugs (NSAIDS) as co-medication. In multivariate analysis the increase in PPI prescription could partly be explained by physicians' characteristics, such as a high number of referrals for endoscopy and a generally above average prescription rate.

Part of the increase in PPI prescription may be explained by the growing demand for gastro protective medication because of the increasing use of non-steroid anti inflammatory drugs (NSAIDS). Long term use of NSAIDS increases the risk of gastrointestinal bleeding, and high risk groups are advised preventive PPI use. In a retrospective cohort study we examined the trends in adequate gastro protection with ASDs of patients at high risk of gastrointestinal bleeding (**Chapter 3**). Of the population in the AHD 7.5% used NSAIDS on a continuous basis. The percentage of high risk patients adequately protected by ASD as co-medication increased between 2001 and 2007 from 40 to 70%. This gastro protective indication contributed to the ASD prescription and might explain 15% of the reported annual increase in ASD. Not all high-risk patients were equally well protected. In multivariate analyses adequate gastroprotection appeared to be associated with longevity (70 +) of the patients, the use of antidepressants, corticosteroids and coumarin as co-medication and with arthritis as co-morbidity. Prescribing policies of GPs and specialists need to be improved for adequate protection of the remaining 30% of the patients at high risk of gastrointestinal bleeding.

In **Chapter 4**, we report a systematic analysis of international publications on the effectiveness of implementation strategies for

ASD prescription optimalisation programmes. A 'systematic review' of randomized trials and cohort studies identified the effects of different intervention methods on prescription behaviour and the associated costs. We identified a total of 10 studies of sufficient methodological quality which studied various combinations of passive and active, and single and multiple implementation methods. The effectiveness of the interventions varied considerably. Passive interventions proved ineffective and the use of active interventions seemed obviously a pre-condition to achieve a reduction of ASD prescriptions. Costs appeared difficult to compare between the different study types. More extensive research is needed to determine the best instruments for successful interventions in changing prescribing behaviour.

Before broad introduction we tested the ASD managed care programme in a pilot setting among 158 GPs in the Amsterdam region (**Chapter 5**). The ASD reduction programme for GPs consisted of a "stop protocol" with a list of chronic users of ASD in the practice of the GPs and patient information material. They were invited for a training seminar, and were offered 3 additional consultations as financial compensation for their efforts. Every three months they received feedback of the patients in their practice who had ceased successfully. GPs were not randomised, and the 267 regional GPs who did not participate in the program formed the control group. After 18 months the number of patients in the intervention group that stopped or decreased the use of ASD was 4.1% higher than in the control group. In the intervention group the annual volume decreased by 9 (Defined Daily Doses) DDDs per patient (OR 0.98) and the total annual costs by 11 Euros (OR 0.97). Although the differences with the control group were modest, this health insurance company initiated programme seemed to stimulate GPs to optimise their ASD prescription policy.

The experiences of patients with the ASD reduction programme in the pilot are described in **Chapter 6**. A questionnaire was sent to a

randomly selected group of 2376 patients chronically using ASD in the pilot region; 54% did respond. The majority (70%) of the patients were willing to participate in the ASD reduction program. Of the patients that were invited by the GP invited to participate (N = 188) 30 (16%) managed to stop using ASD compared with 65 (7%) of the patients that did not participate. A psychometric analysis of three categories of questions about motivation and experiences showed that a majority of the participants were dissatisfied with the support they had received from the GP during their attempt to reduce ASD. Patients felt they had not received enough information about the possible relapse of symptoms after stopping (76%), on the need to improve their life style (68%) and felt insufficiently explained about the need to stop ASD (50%). Better support by the GP might make more patients successfully discontinue their chronic ASD medication.

With the results from the pilot study and the patient survey the ASD reduction programme was improved. In **Chapter 7** we report the effectiveness of the programme after a widespread implementation among nearly 1000 GPs in the Agis region. The GPs, aggregated in peer consultation groups, were randomly distributed over an intervention group that received the adapted protocol by mail, with instructions, list of patients on chronic ASD per practice and patient information material, and a control group that did not receive the protocol. After 6 months the difference between the two groups in the number of patients that decreased the use of ASD with more than 50% was only 0.4% (RR 1.04). The changes in volume and cost also did not clearly differ, 0 DDD (Adjusted $\beta = 0.33$) and 0.4 Euro (adjusted $\beta = 1.63$) per patient, respectively. It was concluded that passive distribution of the ASD reduction programme was not effective. A more active approach seems needed for successful implementation. In the next phase of the implementation of the programme, the effectiveness of two active implementation strategies was compared in a randomized study among GPs (**Chapter 8**). The Implementation was supported by either telephone counselling

or by practice visits by trained project facilitators, and compared with a control group of GPs in which no intervention took place. In a 6 months follow-up the number of patients that decreased ASD with more than 50% in the group that received telephone support was 3.2% higher (RR 1.26), and in the group with practice visits it was 0.4% (RR 0.99) higher as compared to the control group. The 6 months changes in volume and costs were -7.1 DDDs (adjusted β =- 3.01) and -3.4 Euro (adjusted β =- 4.10) per patient in the group with telephone support, versus -6.2 DDDs (adjusted β =- 5.82) and -3.0 Euro (adjusted β =- 3.96) per patient in the group with practice visits. We concluded that implementation of the ASD reduction program with telephone support did cause a significant reduction of ASD prescription, whereas implementation with supportive practice visits did not. The latter result may be due to the fact that visiting all the participating GPs by the facilitators took longer than expected, so the observation time may have been too short to demonstrate an optimal effect. In general, it was concluded that the active implementations of the ASD reduction program had more effect than the passive implementation. Results may further be improved by actively involving patients in the program and supporting the intervention through the involvement of pharmacists or a 'nurse practitioner'.

In **Chapter 9** the potential of the database of Agis health insurance company for scientific research was evaluated. The so-called routine data from the health insurance company prove to be very reliable and to offer good opportunities for in particular etiological and intervention studies. Prognostic studies are also possible, as demonstrated with a number of examples of studies performed with the Agis Health Database. The main limitation of the AHD is the lack of clinical information about the patients. Solutions for this may be the use of proxy indicators or by enriching the database through linkage with data from clinical databases from primary or secondary care.

Finally, in **Chapter 10** we discuss the potential role of the health insurance company in the optimalisation of prescription policies. There is sufficient support among GPs and patients for an active role of the health insurance company, who is well equipped to develop and implement intervention programmes in its network of contracted primary care practices. Although the effects of the Agis ASD reduction program were limited, further refinement of both the programme and the implementation methodology may improve the results. More involvement of patients in the programme is essential, as is monitoring and feedback of prescriptions practice to GPs. In the near future more insurance company initiated intervention programmes will be implemented in primary and secondary care aiming at increasing cost-effectiveness of health care provision.

Nederlandse Samenvatting

Het gebruik van maagzuurremmende medicatie, in de internationale literatuur "acid suppressing drugs " (ASD) genoemd, neemt in Nederland jaarlijks toe met ruim 10%. Het grootste deel (90%) van de ASD medicatie bestaat uit protonpompremmers, en 3,5% van de Nederlandse bevolking neemt dagelijks ASD. De indicaties voor het chronische gebruik van PPIs bij maagklachten zijn vaak niet 'evidence based' en veel patiënten zouden met het gebruik kunnen stoppen of kunnen overgaan op een gebruik alleen wanneer er klachten zijn, een zogenaamd 'on-demand' gebruik.
In de huidige meer op de markt georiënteerde gezondheidszorg hebben de zorgverzekeraars een grote rol in het beheersbaar houden van de kosten en het bevorderen van de kwaliteit in de zorg. Het domein van de farmacie, dat 25% van het nationale zorgbudget inneemt, is daarbij altijd een belangrijk aandachtsgebied geweest. Door gestructureerde zorgprogramma's te implementeren is op dit domein grote kosteneffectiviteitwinst te behalen. Agis zorgverzekeringen heeft tegen deze achtergrond binnen haar regio een zorgprogramma geïnitieerd voor het optimaliseren van het voorschrijfbeleid van ASD. Om de beste introductie methode vast te stellen werd het programma via een aantal verschillende implementatie strategieën uitgevoerd.
Dit proefschrift is het verslag van de wetenschappelijke evaluatie van het Agis ASD optimalisatie programma, waarin is geëvalueerd of het programma tot een verminderd ASD gebruik leidde en of dit kosteneffectief was. In eerste instantie werden een aantal voorstudies gedaan (Hoofdstuk 2 en 3) om de prevalentie van het ASD gebruik en de indicatie ervoor beter in kaart te brengen. Vervolgens werd in de literatuur gekeken naar de meest geschikte methode om het programma te implementeren (Hoofdstuk 4). Daarna werd met een concept programma een pilotstudy onder huisartsen uitgevoerd (Hoofdstuk 5) en de ervaringen van patiënten hiermee geëvalueerd (Hoofdstuk 6). Het uiteindelijke interventieprogramma werd vervolgens op verschillende manieren Agis-breed geïmplementeerd en in een randomised clinical trail geëvalueerd (Hoofdstuk 7en 8). Deze evaluatie vond plaats aan de hand van de gegevens van de

verzekerden uit de Agis Health Database (AHD) en de mogelijkheden van de AHD voor wetenschappelijk onderzoek werden in een breder perspectief geëvalueerd (Hoofdstuk 9).

In **hoofdstuk 2** werd de stijging van het gebruik van farmacotherapie bij maagklachten over drie opeenvolgende jaren geanalyseerd aan de hand van de gegevens uit de AHD. In een cohort van bijna een half miljoen verzekerden werd onderzocht met welke patiënt of voorschrijver gerelateerde variabelen de stijgende trend in PPI gebruik samenhing. De jaarlijkse stijging van 6-10% in PPI gebruik blijkt gecorreleerd te zijn aan leeftijd en geslacht (vooral vrouwen van hogere leeftijd) en met het gebruik van niet-steroïde ontstekingsremmers (NSAIDS) als co-medicatie. In een multivariate analyse kon de stijging van het voorschrijven van PPI slechts in geringe mate "verklaard" worden door artsgebonden kenmerken, zoals een hoog verwijscijfer voor endoscopie en een hoog gemiddeld voorschrijfcijfer.

Als gevolg van een stijging van de prevalentie van aandoeningen van het bewegingsapparaat stijgt ook het gebruik van NSAIDS. Het gebruik van NSAIDS verhoogt het risico op maagbloedingen; reden waarom in hoog risico groepen het preventieve gebruik van ASDS wordt geadviseerd. In **hoofdstuk 3** is in een retrospectieve cohort studie onderzocht in welke mate patiënten met een hoog risico op maagbloedingen adequaat met ASDS beschermd worden. Van de verzekerden in de AHD gebruikt 7.5% NSAIDS op continue basis. Het percentage hoog risico patiënten dat adequaat beschermd is door het gebruik van ASD als co-medicatie steeg tussen 2001 en 2007 van 40 naar 70%. De hierdoor veroorzaakte stijging in ASD prescriptie verklaart 15% van de gesignaleerde jaarlijkse ASD stijging. Niet alle hoog risicopatiënten worden evengoed beschermd. Het krijgen van adequate bescherming blijkt in multivariate analyse samen te hangen met de hoge leeftijd (70+) van de patiënten, het gebruik van antidepressiva, corticosteroïden en coumarine als co-medicatie en met arthritis als co-morbiditeit. Verbetering van het voorschrijfge-

drag van huisartsen en specialisten is nodig om ook de resterende 30% van de patiënten met een hoog risico op een maagbloeding adequaat te beschermen.

In een overzichtsstudie in **hoofdstuk 4** is aan de hand van systematische analyse van internationale publicaties nagegaan welke methoden effectief zijn om een reductie in het voorschijven van ASD te bewerkstelligen. In een ' systematic review' van gerandomiseerde trials en cohort onderzoeken werden de verschillende toegepaste interventies geïnventariseerd en werd nagegaan wat de effecten waren op het voorschrijfgedrag en de daaraan verbonden kosten. In totaal werden 10 studies van voldoende methodologische kwaliteit gevonden, waarin diverse combinaties van passieve en actieve, en enkel- en meervoudige implementatie methoden werden gebruikt. De resultaten liepen sterk uiteen. Passieve interventies blijken weinig effectief en het gebruik van actieve interventies lijkt een voorwaarde om een vermindering van de ASD prescriptie te realiseren. De kosteneffectiviteit blijkt moeilijk vergelijkbaar tussen de diverse studies. Meer grootschalig onderzoek is nodig om vast te kunnen stellen wat de beste interventie instrumenten zijn om voorschrijfgedrag succesvol te beïnvloeden.

Om tot een succesvolle interventie voor het verminderen van het ASD voorschrijven te komen, werd een eerste opzet van het programma geëvalueerd in een pilotstudy in de Amsterdamse regio. In **hoofdstuk 5** is het ontwikkelde ASD reductieprogramma voor huisartsen beschreven. De interventie bestond uit het toesturen van een 'stopprotocol' met een lijst van chronische ASD gebruikers uit de praktijk en een nascholingsseminar. De 158 deelnemende huisartsen kregen ook patiëntenvoorlichtingsmateriaal mee en konden extra consulten in rekening brengen. Om de lke drie en de huisartsen voorlichtingsmateriaal voor de patienten een pilot-studie en onderzocht die een reductie van ASD nasdrie maanden ontvingen zij bericht over de patiënten in hun praktijk die succesvol waren gestopt. De 267 huisartsen die niet deelnamen aan het programma

vormden de controle groep. In de interventie groep was na 18 maanden het aantal patiënten dat het gebruik van ASD stopte of verminderde 4,1% hoger dan in de controle groep. Vervolgens werden in een multivariate regressie analyse de verschillen in het volume (in Defined Daily Doses) en de kosten (in Euro) van ASD bepaald. In de interventie groep was het volume op jaarbasis gedaald met 9 DDDs per patiënt (OR 0.98) en de kosten met 11 Euro gedaald (OR 0.97). Hoewel de verschillen met de controle groep vrij gering zijn, leek een actieve interventie van de zorgverzekeraar toch in staat om huisartsen te stimuleren het ASD voorschrijfbeleid te optimaliseren.

In **hoofdstuk 6** zijn de ervaringen van patiënten met het ASD reductieprogramma beschreven. Onder een willekeurig gekozen groep van 2376 chronisch ASD gebruikende patiënten uit de pilotstudie werd een enquête verspreid; 54% respondeerde. De meerderheid (70%) van de patiënten was bereid aan het ASD reductie programma deel te nemen. Van de direct op uitnodiging van de huisarts deelnemende patiënten (N=188) slaagden er 30 (16%) in te stoppen met ASD gebruik tegenover 65 (7%) van de niet-deelnemende patiënten. Uit een psychometrische analyse van drie categorieën vragen naar ervaringen en motivatie bleek een meerderheid van de deelnemers ontevreden over de ondersteuning die ze van de huisarts hadden gekregen. Patiënten vonden dat ze te weinig informatie hadden gekregen over de mogelijke relaps van klachten na stoppen (76%), over noodzaak tot verbetering van leefgewoonten (68%) en over de noodzaak om ASD gebruik te stoppen (50%). Betere ondersteuning van de huisarts zou mogelijk meer patiënten kunnen doen slagen in hun pogingen te stoppen met ASD.

Met de resultaten uit de pilotstudy en de patiënten enquête werd het ASD reductieprogramma verbeterd. In **hoofdstuk 7** wordt verslag gedaan van de evaluatie van de grootschalige implementatie van dit programma onder bijna 1000 huisartsen in de Agis regio. Daarbij werden de huisartsen, geaggregeerd naar hun collegiale

overleggroep (HAGRO), random verdeeld over een interventiegroep die het programma met aangepast protocol per post ontvingen en een controlegroep die dat niet kreeg.
Na 6 maanden was het verschil tussen beide groepen in het aantal patiënten dat het gebruik van ASD met meer dan 50% verminderde slechts 0,4% (RR 1,04). Ook de verandering in het volume en de kosten verschilde niet duidelijk, respectievelijke 0 DDD (adjusted β=0,33) en 0,4 Euro (adjusted β=1,63) per patiënt. Geconcludeerd werd dat het door de verzekeraar op deze wijze geïntroduceerde ASD reductieprogramma niet effectief is. Een meer actieve benadering van de huisarts lijkt nodig om daadwerkelijk effect te ressorteren.
In de daarop volgende fase van de implementatie van het programma werd het effect van twee actieve implementatie strategieën vergeleken in een gerandomiseerde studie onder huisartsen. De implementatie van het ASD reductie programma, beschreven in **hoofdstuk 8**, werd nu ondersteund door telefonische begeleiding dan wel door praktijkbezoeken van projectbegeleiders. Het aantal patiënten dat het ASD duidelijk (>50%) minderde in de groep die telefonische ondersteuning kreeg was 3,2% (RR 1,26) groter dan in de controlegroep. In de groep met praktijk bezoeken was dat 0,4% (RR 0,99). De verandering in het volume en de kosten in de groep met telefonische ondersteuning en met praktijk bezoeken waren respectievelijk -7,1 DDDs (adjusted β=-3,01) en -3,4 Euro (adjusted β=-4,10), versus -6,2 DDDs (adjusted β=-5,82) en -3,0 Euro (adjusted β=-3,96) per patiënt. Geconcludeerd werd dat het ASD reductie programma met telefonische ondersteuning wel tot een significante daling van ASD prescriptie leidde, maar ondersteuning door praktijkbezoeken niet. Dat laatste resultaat kan het gevolg zijn van het feit dat het bezoeken van alle deelnemende huisartsen meer tijd vergde dan verwacht, waardoor de observatietijd te kort werd om een optimaal effect waar te nemen. In het algemeen werd geconcludeerd dat de actieve implementaties van het ASD reductie programma meer effect hadden dan de passieve implementatie. Grotere effecten zouden verwacht kunnen worden, als de patiënten zelf

actief in het programma betrokken zouden worden en bijvoorbeeld de apotheker of de 'nurse practitioner' ook ondersteuning aan de patiënten zouden geven.

In **hoofdstuk 9** wordt het gebruik van de database van Agis zorgverzekeraar, voor wetenschappelijk onderzoek geëvalueerd. De zogenaamde routine data van de zorgverzekeraar blijken zeer betrouwbaar en bieden goede mogelijkheden voor het doen van in het bijzonder etiologische en interventie studies. Ook prognostische studies zijn mogelijk, zoals blijkt uit een aantal voorbeelden van studies die met de Agis Health Database werden verricht. Een beperking is het ontbreken van klinische informatie over patiënten. Oplossingen hiervoor kunnen gevonden worden door het gebruik van proxy indicatoren of door de database te verrijken middels een koppeling met gegevens uit databases met klinische informatie van bijvoorbeeld de huisarts of het ziekenhuis.

Ten slotte wordt in de afsluitende discussie de rol van de zorgverzekeraar bij het optimaliseren van een kosteneffectief ASD voorschrijfbeleid besproken. Onder huisartsen en patiënten bestaat voldoende steun en draagvlak voor een actieve rol van de zorgverzekeraar. De verzekeraar blijkt goed in staat een interventie programma op te zetten en te implementeren middels een actieve benadering van de huisartsen Het gebruik van de beschikbare database van verzekerden was hierbij essentieel. Hoewel de effecten van het Agis ASD reductie programma beperkt waren zal een verdere verfijning van het programma en de implementatie methoden de resultaten kunnen verbeteren. Belangrijke elementen daarin zijn het meer betrekken van de patiënten zelf in het programma, het monitoren van voorschrijfgedrag aan de hand van 'performance indicators' en intensivering van de feedback naar huisartsen. Dergelijk interventie programma's van de zorgverzekeraar gericht op verhoging van de kosteneffectiviteit , zullen in de toekomst ook toegepast kunnen worden bij andere zorginstellingen in de eerste lijn en het ziekenhuis.

Dankwoord

Wat begon als opdracht van Agis Zorgverzekeringen eindigde in een proefschrift bij het Julius Center. Werd mij aanvankelijk gevraagd de verschillen van antacida-voorschriften tussen huisartsen te monitoren, na verloop van tijd groeide het uit tot een zorgproject over rationeel voorschrijven bij dyspepsie. Contacten met de universiteit over het maken van een 'stopprotocol', stelde mij al snel voor een volgende keuze: het project afronden in een proefschrift. Ik heb dit aanbod met enige aarzeling aanvaard, wetende wat de impact zou zijn op mijn werk en privé. Nadat ik in september 2004 een dag in de week bij het JC introk, heb ik vasthoudend aan mijn proefschrift gewerkt. Terugkijkend heb ik een bijzonder leerzaam proces doorlopen, dat begon bij het bestuderen van veel losse details, maar overging in het op afstand bekijken van het grote geheel en de ontbrekende delen, om conclusies uit een compleet en sluitend onderzoek te kunnen trekken.
Zo'n langdurig proces doorloop je niet alleen. Het wordt geïnspireerd en gesteun door vele anderen.

Een proefschrift kan niet tot stand komen zonder promotor en co-promoter; voor mij Arno Hoes en Niek de Wit. Het drie-traps design waarover we in het begin vaak struikelden en in fraaie schema's op Arno's white-bord uittekenden, hebben we om het nog te kunnen ontwarren op foto vastgelegd. Telkens als we het probeerden te vereenvoudigen, keken we vertwijfeld naar die foto, maar met jullie systematische aanpak kwam dat iedere keer weer een stap dichterbij. Dat vertrouwen in een goede afloop heeft Niek in mijn begeleiding steeds onderstreept. De uiteindelijke weerslag hiervan in de serie artikelen van dit proefschrift heeft veel discussie geëist, maar de uiteindelijke Engelse versies zijn er wel stukken op vooruit gegaan. De exercitie is nu gedaan, maar de discussie niet; die gaat gelukkig gewoon door.

Agis heeft dit proefschrift niet alleen materieel mogelijk gemaakt, maar herbergde ook de collega's die onmisbaar waren voor het tot stand komen ervan. De Agis Health Database vormde het

fundament van het onderzoek en zonder de hulp van Ignace en Henk was de ontsluiting en bewerking van deze data voor mij een onneembare barrière gebleven. Jullie werden er gelukkig niet wrevelig van als ik weer met nieuwe analysevragen kwam, en ook Paul en Gea waren altijd bereid mij even snel aan nieuwe gegevens te helpen.
Het slagen van de grote trial, was geheel afhankelijk van onze 'pratice facilitators' Gelukkig hebben Esther, Silfke en Sander alle tijd genomen, net zo lang totdat zij met alle huisartsen over het project gesproken hadden. Ik waardeer des te meer, dat jullie hiervoor een spoedcursus reflux-gerelateerde ziekten hebben moeten volgen.
Net zo belangrijk waren de instigatoren van het kosteneffectief voorschrijven, Francine en Paul die het maagzuurremmerproject in de steigers zetten en op een Agis-brede uitvoering aanstuurden. Jullie hebben mij samen met Arnold bovendien volledige morele steun gegeven om het project voort te zetten in een proefschrift en zelfs bij de directie RVVZ-gelden weten vrij te krijgen voor de 'evaluatie van het project'. Arnold is mijn steun en toeverlaat geworden als schakel tussen Agis en het JC, maar ook persoonlijk heb ik veel gehad aan de rust waarmee jij alles in goede banen leidde.

Geen project zonder praktijk. Hoewel de huisartsen in het proefschrift als weerbarstig worden afgeschilderd en mijn hoge verwachtingen om minder voor te schrijven enigszins afstraften, wil ik alle huisartsen in de Agis-regio bedanken voor hun medewerking. 1417 huisartsen waren er teveel om allemaal te kunnen ontmoeten, maar in meerderheid hebben jullie positief op ons project gereageerd. Ik hoop dat het rationeel voorschrijven een punt van jullie aandacht blijft.

Het Julius Center is mijn thuisbasis geworden, niet alleen voor het maken van dit proefschrift, maar ook voor mijn dagelijkse werkzaamheden. Hier vond ik in overvloed van alle collega's om mij

heen de benodigde intellectuele prikkels. Het sparren met Peter over de statistiek heeft daarin een speciale 'catch' gekregen. Door jouw uitleg ging mijn kennis over multi-levelen met sprongen vooruit en jouw analyses gaven me zekerheid over de uitkomsten. Van alle collega's zag ik mijn kamergenoten natuurlijk het meest. Alike, Rhea, Suhreta, Mirjam en Wijnand hebben mij een vruchtbare werkomgeving gegeven en jullie waren er ook als ik mijn hart wilde luchten over het moeizame proces van een proefschrift, zodat ik weer moed kon putten uit jullie ervaringen. Ook het samenwerken aan een artikel leer je met je collega's en daarvoor wil ik apart Charles bedanken. Je bent als stagiaire komen aanwaaien, maar het werd voor mij de meest prettige ervaring in samenwerking, met als resultaat een prachtige publicatie.

Voor de wekelijkse portie afreageren stonden mijn judomaten klaar. Te laat komen omdat het boekje nog niet af is, geldt nu niet meer als smoes en jullie vinden dat ik weer serieus aan mijn 3e Dan moet werken. Erik, fijn dat je samen met Frank de cover en de opmaak wilde ontwerpen en er een mooi boekje van hebt gemaakt. Het is een juweeltje.

Tegen mijn familie kan ik nu zeggen dat mijn 'vierde studie' helemaal af is en dat ze het kunnen nalezen in het boekje. Mijn broers en zuster zullen wel denken: zou hij nog aan een vijfde beginnen op zijn leeftijd. Aan mijn moeder, die altijd dacht dat ik dokter zou worden, zal ik nu vertellen dat ik doktor geworden ben en ze zal me vragen of ik nu meer tijd heb. Mijn kinderen, René, Myrte en Sarah, wil ik met dit boekje meegeven dat jullie ook kunnen bereiken wat je wilt, als je maar in jezelf gelooft dat het lukt. Tegen mijn vrouw Daisy wil ik zeggen: blij dat dit avontuur afgelopen is en ik je geduld niet langer op de proef hoef te stellen. Je vindt dat je alles uit jezelf moet halen wat er in zit en hebt regelmatig met peper gestrooid. Samen met je morele steun en persoonlijke betrokkenheid heeft mij dat enorm geholpen om het tot een goed einde te brengen.

Curriculum Vitae

Hugo Matthias Smeets (1954, Heerlen) studied social science and medicine at the University of Utrecht and graduated in 1983 and 1984, respectively. From 1984 he worked for the department of Health Services of the municipality of Utrecht to improve cooperation between care providers in Primary Care. In 1988 he went to the VU Medical Center in Amsterdam to conduct research in the surgical department of the hospital with a focus on transitional care. During this time he was also trained in clinical epidemiology and obtained his masters in 1992. From 1993 to 1996 he worked as an epidemiologist for several Community Health departments on public health issues. In this period he was also medical coordinator and researcher for Medicine sans Frontières (Doctors without Borders) in conflict areas (Albania, Congo Br., Somalia) to initiate and evaluate field projects. At the end of 1996 he started research work for Silver Cross Health Insurance Company and became research advisor for Agis Health Insurance Company in 2000. In this position he started collaboration with the Julius Center for Health Sciences and Primary Care of the University Medical Center in Utrecht and initiated scientific research with data from the Agis Health Database (AHD). In 2007 he joined the Julius Center to actively conduct research with the AHD in a project on antibiotic prescriptions and coordinated many other research projects with the AHD. He was appointed as coordinator of the Utrecht Primary Care Network (HNU) and the regional Mental Health Case Register (PCR), meanwhile finishing his thesis on acid suppressing prescription of general practitioners. He now has a management position in the Julius Center to initiate research on (linked) routine databases.