The ever increasing use of acid suppressive therapy

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The ever increasing use of acid suppressive therapy. Descriptive analysis of data from the national wholesale and prescription databases on the consumption of proton pump inhibitor in Norway.

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Sammanfattning

Farmakoepidemiologiske analyser er nødvendige som bakgrunn for å evaluere legemiddelbruk og gjøre kostnads-effektivitets prioriteringer. Databaser med informasjon om salg og forskrivning av legemidler er nyttige redskaper for slike analyser.

I denne oppgaven presenteres en analyse av salgs- og forskrivningsdata for protonpumpehemmere, en legemiddelgruppe som brukes ved syrerelaterte gasterointestinale sykdommer.

Forbruket av protonpumpehemmere i Norge har siden 1996 økt med 10 % per år, med esomeprazol som vanligste legemiddel. Et økende antall personer bruker disse legemidlene. Utgiftene for det offentlige trygdesystemet er omfattende, mer enn 450 millioner NOK i 2006. Verifisert spiserørbetennelse er den dominerende årsak til forskrivning angitt på reseptene. Det er indikasjoner på en for høy forskrivning av protonpumpehemmere. Forskrivningen i Norge er forskjellig fra Danmark og Sverige, både med hensyn på valg av legemiddel og forbruksnivå.

Prevalens for bruk av protonpumpehemmere øker med alder og når et maksimum på nær 12 % av befolkningen i aldersgruppene 70-79 og 80-89 år. En betydelig andel bruker legemidlene over lengre tid (> 2 år). Dette er grupper som bruker mange legemidler samtidig (polyfarmasi). Selv om protonpumpehemmerne har vært på markedet i mange år, diskuteres fortsatt negative følger av langtidsbruk og det er behov for å studere bruken nærmere. Oppmerksomheten bør rettes mot rasjonell bruk av disse legemidlene, ikke bare hvordan utgiftene til dem skal kunne reduseres.

Nyckelord

Farmakoepidemiologi, registerstudier, reseptstatistikk, protonpumpehemmere

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Abstract
Pharmacoepidemiological analyses are needed as a background for evaluation of drug use and for making cost-effective priorities. Drug sales and prescription databases provide useful tools for analysis of drug consumption and expenditures.

In this essay, an analysis of the sales and prescribing of proton pump inhibitors (PPIs), drugs used for acid related gastric disorders, are presented.

Since 1996, the consumption of PPIs in Norway has increased by approximately 10 % per year, with esomeprazole as the most commonly used drug. An increasing number of individuals are using these drugs with considerable costs for the reimbursement schemes, e.g., in 2006 more than 450 million NOK. Verified reflux oesophagitis is the predominant indication for reimbursement prescribing. There are, however, indications of an overprescribing of PPIs. The prescribing in Norway is different from Denmark and Sweden, both regarding choice of drug and level of consumption.

The prevalence of PPI use increased with age, reaching a maximum of nearly 12 % in the age groups 70-79 and 80-89 years of age. A considerable proportion is long-term users (> 2 years). These groups have a high risk of polypharmacy treatment. Even though the PPIs have been on the market for many years, negative effects associated with long term use are being discussed and need to be further explored. Attention should be focused on the rational use of PPIs and not only on the reduction of costs for PPI therapy.

Key words
Pharmacoepidemiology, register studies, prescription statistics, PPIs

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1 INTRODUCTION

It is recognised that the resources available to meet health care needs are limited. The Norwegian health authorities aim to use the allocated funds for health services as cost-effectively as possible, by reducing the costs, if possible, without reducing the quality of the services available to the patients.

Detailed knowledge on the consumption of drugs is needed as a background for evaluation of drug use and for making cost-effective priorities. Drug sales and prescription databases are useful tools for an overview of drug consumption and expenditures. In Norway, the two most important ones are the Norwegian Drug Wholesaler Database (NorDWD), which contains the sales of all drugs to pharmacies, hospitals and non-pharmacy outlets, and the Norwegian Prescription Database (NorPD), which contains all the prescriptions dispensed in the pharmacies. Both databases are administered by the Norwegian Institute of Public Health, Department of Pharmacoepidemiology, and are under the pursuance of Norwegian law. These databases provide the health authorities with the relevant statistics and background for the evaluation of the reimbursement scheme.

In 2006, the pharmacological group Proton Pump Inhibitors (PPI), acid suppressing drugs indicated for gastric acid-related diseases, accounted for a total sale of nearly 453 million NOK. Of this 93%, was covered by public reimbursement scheme. The main indication for reimbursement is confirmed reflux oesophagitis. An overuse of acid suppressing therapy is, according to the medical literature, well documented (1;2). The PPIs are one of several groups of drugs being scrutinized by the health authorities.

Analyses of data from register databases are essential for the decision-making and follow-up of prescribing. The analyses of the PPIs can also be used as a model for analyses of other groups of drugs. The two databases, NorDWD and NorPD, can provide a background for an evaluation of the prescribing and use of PPIs. The databases make it possible to follow the development of consumption over time, as well as, provide a description of the users.

2 OBJECTIVES

The main aim of this study was to perform a descriptive analysis of data from the NorDWD and the NorPD which provide information on sales, prescription pattern and use of PPIs in Norway.

Specific objectives were to analyses and present:

- development of sales and prices over time
- prevalence and incidence of PPI use
- long-term user
- adherence to therapy

- reimbursement indications as stated in the prescriptions

An additional objective was to compare the sale of PPI with corresponding data from Sweden and Denmark.

The analyses may serve as a background for an evaluation of PPI prescribing, including reimbursement criteria and the rational use of PPIs.

3 BACKGROUND

3.1 The reimbursement system in Norway

The Norwegian reimbursement scheme

In 2006, more than 900 000 individuals, almost 1/5 of the Norwegian population, could be defined as heavy consumers of health services paid for by the Norwegian National Insurance Administration (NNIA). In this context, a heavy consumer is one that has reached a co-payment of at least 1615 NOK a year on drugs and certain health services recognised by the NNIA and an attainment of 1615 NOK triggers the entitlement to recieve a “free card”. The free card means no more co-payments for these services for the remaining of the calendar year (3).
The number of “free cards” has nearly doubled since 1998. In 2005, the total expenditures on health services for NNIA reached 4 481 billion NOK, of which drugs and medical equipment accounted for 1 846 billion NOK (41%).

Controlling the cost of drugs and improving the functionalities of the reimbursement system are ways to reduce costs for NNIA. By introducing new pricing systems and conducting evaluations of the reimbursement system in general, especially of important therapeutical groups such as statins and antihistamines, the insurance system has managed to somewhat halt the rise in expenditures for drugs in 2005. However, continuous evaluation and follow-up is necessary.

The reimbursement scheme is an important tool for the achievement of political health goals regarding social security and welfare for the citizens. One of these goals is that everyone should have access to necessary medicines, regardless of their ability to pay. Membership in the National Insurance programme is mandatory for all Norwegian citizens.

Nearly 10 billion NOK, or 67% of the costs for prescription-only medicine, are born by the Norwegian National Insurance Administration (4).

The basis of the reimbursement scheme is a list of diseases/conditions, developed over time. Each of the diseases/conditions has defined criteria for reimbursement and a corresponding positive list of reimbursable drugs (5).

The lists of diseases/conditions are part of the Norwegian legislation and can only be changed by the Ministry of Health and Care Services. The levels of the diseases and conditions are not comparable and varies from specific (e.g., diabetes mellitus) to very broad (e.g., cardiovascular diseases) categories, reflecting the way the list has evolved in steps over the years. Table 1 provides an overview of the most important reimbursement diseases/conditions (code number of the disease/condition from the legislative list is given in brackets).

A requirement for inclusion in the list is that the disease/condition is serious and chronic with a need for "long-term treatment". This long-term treatment is defined as more than 3 months per year. Drugs on the list must have a Marketing Authorisation (MA). Reimbursement is only granted for indications approved for the drug in the Summary of Product Characteristics (SPC), and the holder of the MA has to apply for inclusion in the reimbursement scheme. Since 2002, documentation of cost-effectiveness, as compared to alternative treatment, has been mandatory in reimbursement applications. The Norwegian Medicines Agency decides whether or not an application for inclusion in the reimbursement programme should be granted (6).

In addition to the general reimbursement scheme, patients have the opportunity to apply for reimbursement on an individual basis for diseases/conditions and drugs not included in the list, according to a set of criteria. In 2006, these individual reimbursements accounted for approximately 10% of the total costs. The reimbursement scheme also covers a selection of medical equipment.

Disease/condition (code number according to list)	Mill NOK	% of total
Cardiovascular diseases (12)	2316.5	29.9
Depressions and psychiatric diseases (18)	877.1	11.4
Asthma and obstructive lung disease (2)	686.1	8.9
GORD (41)	**402.4**	**5.2**
Diabetes (5)	392.6	5.1
Cancer and malignancies (9)	383.2	5.0
Epilepsy etc (7)	329.7	4.3
Allergy (33)	311.0	4.1
Migraine (36)	255.9	3.3
Hormonal failure (6)	186.1	2.4
Other diseases/conditions (§ 9)	1530.2	19.9
Total	7670.7	100

Table 1: The 10 most common diseases/conditions in the general reimbursement scheme (§ 9 in the "Blåreseptforskriften" – the regulations for reimbursement) in 2006, as determined by turnover in millions NOK. Source: Apotek og legemidler 2007, Apotekforeningen (4).

The relatively well-defined disease/condition GORD (code number 41) is the 4th largest group on the list, only surpassed by the more broad and common disease groups cardiovascular diseases, depressions and psychiatric diseases, asthma and obstructive lung disease.

The patient's co-payment for reimbursed drugs is 36% of the total price of the prescription with a maximum limit of 500 NOK per prescription, a prescription being any number of drugs prescribed by the same physician on the same date and covering drugs for up to three months consumption. There is a ceiling for the total co-payment per year. In 2006, this ceiling was 1615 NOK. The co-payment also includes visits to physicians, laboratory tests, and diagnostic x-rays. When reaching the co-payment ceiling, the patients are entitled to a "free card", which exempts them from further co-payments for the remainder of the calendar year.

The reimbursement system is currently under revision. The first step will be a revision, with the aim of creating a more comprehensible list where diseases and conditions are better integrated with the list of reimbursable drugs. Simultaneously, there is an ongoing review of the reimbursable drugs for the most important diseases. Until now, the statins (lipid lowering drugs), antihistamines and asthma/obstructive lung disease drugs and acid suppressing therapy for GORD have been reviewed. The review of the GORD and PPIs was completed in January 2007.

3.2 The Anatomical Therapeutic Chemical (ATC) and Defined Daily Dose (DDD) methodology

A standardized, validated methodology for the classification of drugs and the measurement of drug consumption is essential in drug utilisation research.

Drug utilization research was defined by WHO in 1977 as "marketing, distribution, prescription, and use of drugs in a society with special emphasis on the resulting medical social and economic consequences"(7).The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve the quality of drug use. Use of the ATC/DDD system allows standardisation of drug groupings and a stable drug utilization metric to enable comparisons of drug use between countries, regions, and different health care settings, and to examine the trends in drug use in different settings over time.

The system has a history that starts as far back as the 1960s. In 1996, WHO decided on globalizing the Division of Drug Management and Policies, and established WHO International Working Group for Drug Statistics Methodology. The ATC/DDD system was chosen as the recommended methodology. An international working group and a collaborating centre were established for the maintenance and further development of the system. The working group comprises 12 members drawn from the WHO Expert Advisory Panels for Drug Evaluation and for Drug Policies and Management. The members have professional backgrounds, which include clinical pharmacology, clinical

medicine, international public health, drug utilization and drug regulation and who represent different users of the ATC/DDD system, as well as different nationalities.

The WHO Collaborating Centre for Drug Statistics Methodology is situated at the Norwegian Institute of Public Health and is financed by the Norwegian Government (8).

3.2.1 ATC

In the Anatomical Therapeutic Chemical (ATC) classification system, the drugs are divided into different groups mainly according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.

Drugs are classified in groups at five different levels. The system is hierarchical. The drugs are divided into fourteen main groups at the 1st level, with pharmacological/therapeutic subgroups at the 2nd level. The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level represents the chemical substance.

The complete classification of omeprazole illustrates the structure of the code:

A	Alimentary tract and metabolism (1st level, anatomical main group)
A02	Drugs for acid related disorders (2nd level, therapeutic group)
A02B	Drugs for peptic ulcers and gastro-oesophageal reflux disease (GORD) (3rd level, therapeutic group)
A02BC	Proton pump inhibitors (4th level, pharmacological subgroup)
A02BC01	Omeprazole (5th level, chemical substance)

Thus, in the ATC system, all plain omeprazole preparations are given the code A02BC01.

3.2.2 DDD

The basic definition of DDD is:

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (8).

The DDD is a unit of measurement for drug utilisation purposes and does not necessarily reflect the recommended or Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will have to be based on individual characteristics (e.g., age and weight) and pharmacokinetic considerations.

Drug consumption data presented in DDDs provide a rough estimate of consumption. The DDDs provide a fixed unit of measurement independent of prices and formulations making it possible to assess trends in drug consumption as well as, perform comparisons between population groups, groups of drugs and the different substances within the groups of drugs.

Very often, the DDD will be a compromise based on a review of the available information, including doses used in various countries. Sometimes the DDD is a dose that is rarely, if ever, prescribed, because it can be an average of two or more commonly used available dose sizes. For esomeprazole, one of the PPIs, the DDD is 30 mg, while the product is marketed in the tablet strengths of 20 mg and 40 mg.

Drug consumption figures are often presented as numbers of DDDs/1000 inhabitants/day. Sales or prescription data presented in DDD/1000 inhabitants/day may provide a rough estimate of the prevalence of drug use in a defined area. For example, the figure 10 DDDs/1000 inhabitants/day indicates that 1% of the population, on average, receive a certain treatment daily.

3.3 Data sources on drug utilisation for pharmacoepidemiological research

Pharmacoepidemiology is defined as the study of the use and effects of drugs in populations (9). Pharmacoepidemiological research can be divided into two main fields (10;11). The first are studies on the variation of drug use in populations, drug use patterns, identification of predictors for use, generation of hypotheses exploring variations, and the public health impact of drug use. The second field includes follow-up studies; e.g., side effects, or post marketing studies investigating long-term effects of specific drugs in a population setting. The analysis in the present study belongs to the first of these main fields.

The Nordic countries have a long tradition in establishing and maintaining national, high quality databases used for pharmacoepidemiological purposes. In Norway, there

are two national databases available to: 1) explore the sales of drugs in a population and 2) and give a description of the users:

- NorDWD covers all sales of drugs with market authorisation from wholesalers to pharmacies. In addition, the database contains sales of drugs without Market Authorisation (MA) and non-prescription drugs sold from wholesalers to non-pharmacy outlets. Drugs are classified according to ATC classification and consumption is measured in DDDs.

- NorPD contains individualised prescription data, with complete information on prescriptions dispensed from all the pharmacies in Norway whether reimbursed or not.

Both databases are hosted by the Norwegian Institute of Public Health.

3.3.1 The NorDWD

Statistics from the NorDWD offer simple, but important, tools for exploring drug use, performing health economic evaluations, and for suggesting appropriate regulatory changes, campaigns etc.

The statistics can be used to:

- survey consumption, and hence therapy, at different levels, as well as, over time
- measure the effect of legislative changes and informational efforts
- define needs for further investigation of drug therapies

However, some limitations should be kept in mind. All drugs sold from wholesalers are not necessarily consumed, and sales intended for the use in the general practice and institutions are at present not treated separately in the statistical material. In addition, variations in population structure (age, sex), number of prescribers, pharmacies and hospitals are not considered.

Overviews of drugs ranked according to their sales in value or volume can easily be retrieved from these statistics (Table 2).

ATC code	Active substance	Indication	Million NOK (AUP)	Million DDD
L04AA11	Etanercept	Arthritis etc	434	1,1
C10AA05	Atorvastatin	Lipid lowering	377	86
R03AK06	Salmeterol and other drugs for obstructive airway diseases	Asthma/COLD	350	21
A02BC05	**Esomeprazole**	**GORD**	**349**	**28**
L04AA12	Infliximab	Arthritis etc	260	1,2
N05AH03	Olanzapine	Psychiatric disorders	208	4,7
C07AB02	Metoprolol	Heart and coronary disorders	199	40
R03AK07	Formeterol and other drugs for obstructive airway diseases	Asthma/COLD	194	11
C10AA01	Simvastatin	Lipid lowering	180	144
C09DA01	Losarten and diuretics	Heart and coronary disorders	168	21

Table 2. The 10 most sold prescription drugs in 2006 ranked according to the sales in millions NOK (pharmacy retail price). Source: Legemiddelforbruket i Norge 2002-2006 (12).

The most sold PPI, esomeprazole (Nexium®), is the 4th most sold of all prescription drugs in Norway according to costs, and is surpassed by the immunosuppressive arthritis drug etanercept (Enbrel®); the lipid lowering drug atorvastatin (Lipitor®); and almost equal to the asthma and COLD combination for inhalation of salmeterol and fluticason (Seretide®).

3.3.2 The NorPD

The prescription statistics from large computerized pharmacoepidemiologic databases with individual identification make it possible to study drug utilization with the individual user as the unit of analysis and provide important research possibilities (13).

In 2003, the Norwegian government decided to establish a national register based on computerised prescriptions dispensed at all pharmacies. The aims of NorPD are pharmacoepidemiologic/pharmacoeconomic research and surveillance of drug utilisation.

According to the legislation, the main purposes of NorPD are to collect and prepare data on drug utilisation in human individuals and animals according to species in order to:

1. Describe drug utilisation in the population, including changes over time
2. Form a basis for and promote the research of the safety and effectiveness of drug use
3. Provide the authorities with an administrative tool to assure high quality of prescribing, in addition to being a tool for supervision, control and planning on a non-individual level
4. To improve quality of prescribing as a part of an audit method by providing the prescribers a basis for reviewing their own prescribing.

The Norwegian Institute of Public Health receives on a monthly basis electronic data on prescriptions from all of the approximately 570 pharmacies in Norway. NorPD contains information of all prescription drugs dispensed at pharmacies to individual patients not living in institutions. The identities of patients and prescribers are encrypted. Each record contains a unique person-identifier, making it possible to identify all prescriptions over time for any given individual, and any given prescribers. The use of drugs bought over the counter is not recorded in NorPD.

In 2006, 3.2 million patients with at least one prescription were recorded in NorPD. This represents 68% of the Norwegian population and a total of 26 million dispensed prescriptions. This registry is an important source for longitudinal studies and record-linkage studies with health surveys and other databases in Norway. NorPD covers the entire nation, 4.6 million inhabitants, and offers unique possibilities for pharmacoepidemiological research and a sound basis of knowledge for national decision-making in the field of drug utilisation.

In addition to individual prescriptions to patients, the database contains the prescribing of drugs to be used in the physicians' own practice, institutions and veterinary prescribing.

3.3.3 Other drug databases in the Nordic countries

The annual publication from NOMESCO, *Health Statistics in the Nordic Countries*, also comprises sales statistics for the Nordic countries for some drug groups. A special publication concerning medicines consumption, *Medicines Consumption in the Nordic Countries 1999-2003,* was published in 2004. This report is a follow-up to the theme section of *Health Statistics in the Nordic Countries 1999* and the report is published on the Internet (14)

Denmark and Sweden have prescription registers similar to the NorPD. The Swedish register on prescribed and dispensed medicines, Swedish Prescribed Drug Register, was established in July 2005. The register contains data with unique patient identifiers for all the drugs dispensed to the entire population of Sweden (15).

In Denmark, there is one national and two local prescription registers. The national register encompasses the entire country and is managed by the Danish Medicines Agency with a history dating back to 1994 (16). In addition there are two local registers: The Odense University Pharmacoepidemiological Database (OPED) and the Pharmacoepidemiological Prescription Database of North Jutland (PDNJ). Together these two registries cover approximately one million, or 18%, of the Danish population and are representative of the Danish population in general. The registries cover all reimbursed medicine at the level of the individual user, with a unique and permanent personal identifier enabling the compilation of longitudinal drug histories and linking of prescription data to other population-based Danish registries (17;18).

Island does not publish official statistics of drug consumption, neither in print nor on the Internet (Mimir Arnorsson, Icelandic Medicines Control Agency, personal communication). In Finland, information regarding drug wholesale and prescription statistics of drugs paid by the National Health Insurance are published on an Internet page (19).

3.4 Epidemiology and treatment of GORD, dyspepsia and gastric ulcers

A variety of diseases are associated with excessive secretion of gastric acid. The most common are dyspepsia, gastroesophageal reflux disease (GORD) and gastric ulcers.

3.4.1 Dyspepsia

Dyspepsia refers to a group of upper gastrointestinal tract symptoms that occur commonly in adults. Dyspepsia may result from organic causes, however the majority of patients suffer from non-ulcer or functional dyspepsia. Epidemiological data from population-based studies in various geographical locations provide some information on prevalence. Population-based studies on true functional dyspepsia (FD) are few, due to the difficulties of conducting such studies. Globally, the prevalence of uninvestigated dyspepsia (UD) varies between 7% and 45%, depending on the definition used and geographical location, whilst the prevalence of FD has been noted to vary between 11% and 29.2%. Risk factors for FD have been shown to include underlying psychological disturbances. It has been shown that females are more at risk. Other relevant risk factors are tied to environment or lifestyle. These include such elements as poor socio-economic status, smoking, increased caffeine intake and ingestion of non-steroidal anti-inflammatory drugs. Both dyspepsia and FD are common conditions globally (20).

3.4.2 Gastro oesophageal reflux disease (GORD)

In American medical literature GORD is referred to as GERD - gastro esophageal reflux"[MeSH Terms]. According to a systematic review of the epidemiology of GORD with strict adherence to criteria for quality of the studies and disease definition, a prevalence of approximately 10-20% has been identified for GORD. GORD is defined

as having at least weekly heartburn and/or acid regurgitation. The incidence in Europe, USA and Australia was approximately 5 per 1000 person years. A number of potential risk factors co-morbidities are associated with GORD, e.g. immediate family history of obesity, respiratory diseases and chest pain (21;22).

3.4.3 Gastric ulcers

The association between Helicobacter pylori infections and gastric ulcers is well documented (23). However, the proportion of ulcers not associated with Helicobacter pylori infection seems to be increasing. A recent review of medical literature indicated that up to 52% of duodenal ulcers and 47% of gastric ulcers are not caused by H. pylori infection. The cause of H. pylori-negative ulceration appears to be multifactorial, with contributing factors including increased use of non-steroidal anti-inflammatory drug, false-negative H. pylori tests and genetic predisposition. H. pylori-negative ulcers tend to be associated with hypersecretion and can have serious clinical consequences.

H. pylori-negative ulcers are often refractory to treatment. PPIs appear to effectively treat the symptoms of both H. pylori-positive and H. pylori-negative ulcers (24).

3.5 Proton Pump Inhibitors (PPIs)

To be able to analyse drug consumption data, a basic background on history, indications, and use of the drugs are necessary.

PPIs are classified in the ATC system and DDDs are assigned as follows (25):

A	Alimentary tract and metabolism
A02	Drugs for acid related disorders
A02B	Drugs for peptic ulcer and gastroesophageal reflux disease (GORD)
A02BC	Proton pump inhibitors

ATC-codes	**DDD**	**Unit**	**Administration route**	**Brand names**
A02BC01 Omeprazole	20	mg	Oral	Losec® **and generics**
A02BC02 Pantoprazole	40	mg	Oral	Somac®
A02BC03 Lansoprazole	30	mg	Oral	Lanzo® **and generics**
A02BC05 Esomeprazole	30	mg	Oral	Nexium®

A02BC04 Rabeprazole is not marketed in Norway.

The first proton pump inhibitor, omeprazole, was launched in 1987. In 2006 there were four substances belonging to the PPI group on the Norwegian market.

In 2005, esomeprazole (Nexium®) was the 3rd most sold drug on the world market with a turnover of US$ 5.7 billion (ex-factory price) and a growth of 16.7% from 2004 (26).

3.5.1 Pharmacotherapy

PPIs are potent suppressors of gastric acid (27). They are used for a variety of upper gastrointestinal tract disorders, especially gastroesophageal reflux (GORD) (28). Several governmental advisory bodies have issued guidelines for the treatment of GORD, dyspepsia and related disorders (29-31).

According to experts, indications for PPIs should be 1) verified GORD with severe symptoms, 2) gastric ulcer and 3) prevention of ulcer occurring as an adverse effect of treatment with NSAIDs. For eradication of Helicobacter pylori, the PPIs are used for short-term treatment in combination with antibacterials. The most common treatment is a combination of a PPI with amoxicillin and methronidazole for 7 days.

According to the guidelines referred to above, mild GORD, non-ulcer dyspepsia with mild symptoms or non-acid related symptoms should not be treated with PPIs.

3.5.2 The different PPIs

The approved indications for the different PPIs are basically similar. No major pharmacological differences are postulated or documented. Equipotency documentation is incomplete and the dosages of PPIs for the different indications are decided according to documentation from the clinical studies conducted by the marketing companies (32).

Omeprazole
Omeprazole was the first PPI on the world market. Until 1996, it was the only PPI, with the trade mark Losec®. In 2001, Losec® lost its patent protection and several generic omeprazole preparations are now available. However, there have been several controversies and court trials regarding specific pharmaceutical formulations of the substance. In 1998, the marketing company, AstraZeneca AB, launched and patented the MUPS (Multiple Unit Pellet System), containing a large number of small individually enteric-coated micropellet tablets, and withdrew other formulations from the market. This resulted in patent controversies that halted the launching of generic omeprazole. In 2003, the strength 40 mg was removed from the world market without explanations from the market authorisation holder (see discussion below).

Pantoprazole
In Norway, the trade mark Somac® was launched in 1996. It is still under patent protection. No generic alternatives are currently available.

Lansoprazole
In Norway, the trade mark Lanzo® was launched in 1998. The substance lost its patent protection in 2005 and generic alternatives are now available. Only the generic alternatives are now available for reimbursement prescribing.

Rabeprazole is not marketed in Norway

Esomeprazole

In 2000, esomeprazole was marketed under the brand name Nexium®, and is still under patent protection. Esomeprazole is the S-isomer of omeprazole, which is a racemate. Normally, when one enantiomer (i.e. the active as compared to the racemate), is developed and marketed, dosage is reduced accordingly. The documentation of the pharmacological activities of the S-enantiomer compared with the racemic esomeprazole/omeprazole is, however, confusing. Nexium® is marketed as 20 and 40 mg tablets; whereas, omeprazole is marketed as 10 and 20 mg tablets. There is no documentation to indicate that the S-enantiomer has a weaker pharmacological effect per mg than the racemate (33;34). If esomeprazole should be regarded as the active enantiomer, the logical strength would be half the strength of omeprazole. However, the holder of the market authorisation, who also originally launched omeprazole, has not conducted studies comparing the equipotency between esomeprazole and omeprazole (30).

3.5.3 Rational use

Results from a qualitative study in the UK indicate that the GPs in the study had a good understanding and knowledge of the issues surrounding PPI prescribing. There are, however, considerable controversies as to how the knowledge reflected in the guidelines should be translated into practice (35).

A review made by the Swedish Pharmaceutical Benefits Board (LFN) has resulted in recommendations regarding first choice therapy. This has led to the decision to remove several of the more costly of the PPIs from the reimbursement scheme. This revision is estimated to provide savings of 175 SEK million annually for the Swedish reimbursement scheme (36).

An overuse of PPIs is documented both in hospital settings and primary care. In Sweden, the increase in the prescribing of PPIs over the last years is described as dramatic. It is postulated that less than half of the prescribing are for the treatment of verified ulcer or GORD, while the remaining is for the treatment of unspecific dyspepsia. Unspecific dyspepsia is one of the most common ailments in primary care (2).

Some studies indicate that discontinuation of therapy with PPIs is complicated even when there may be no definite indication, since a hypersecretion is observed already after 2 weeks treatment and last for up to 6-8 weeks. Long term treatment with PPIs are common (37;38).

3.5.4 Conditions and criteria for reimbursement of PPIs in Norway

The conditions for reimbursement of PPIs in Norway are as follows:

Endoscopically verified reflux esophagitis, or pathological reflux verified by 24- hour's pH measurements, in patients with long lasting severe symptoms.

The prescribing should be instituted by a specialist or in a hospital. The prescribing may be continued by a GP.

In addition, one of the PPIs, omeprazole, is reimbursed when prescribed for prevention or healing of NSAIDs related gastric ulcers. PPIs prescribed in combination with antibiotics for the eradication of Helicobacter pylori are not a reimbursement indication. Unspecific dyspepsia is not an approved indication for PPIs and, thus, not a reimbursement indication.

The Norwegian Health Authorities have revised the reimbursement conditions. As part of this, the Norwegian Knowledge Centre for the Health Services has conducted a review of the medical literature on the effects of drugs in the treatment of GORD. This centre is organised under the Ministry of Health and Care Services as a professionally independent organisation. The Centre has no authority to develop health policy and no responsibility to implement policies.

Only indications approved for reimbursement were reviewed. In the report, the PPIs are compared with alternative therapies for GORD, the H2 receptor antagonists, which are, at present, generally regarded as less important in the treatment.

The report presents the following conclusions (30):

> • A consistent finding is that the PPIs give a faster and more efficient relief of symptoms compared to H2 receptor antagonists, both in acute and long-term, prolonged treatment.
>
> • No differences are demonstrated between omeprazole, lansoprazole, or pantoprazole in the relieving of symptoms and the healing of esophagitis.
>
> • Esomeprazole 40 mg demonstrated a better effect when compared to omeprazole 20 mg and lansoprazole 30 mg. In the treatment of erosive GORD, esomeprazole 40 mg had a higher healing rate after four and six weeks as compared to omeprazole 20 mg.
>
> • The included studies did not present sufficient documentation to conclude possible differences between esomeprazole 40 mg and pantoprazole 40 mg.
>
> • Limited documentation is available regarding the long-term, comparative effects.
>
> • Comparative studies with short follow-up indicate that serious adverse effects are few and that the drop-out frequency, due to adverse effects is low. No consistent differences between the different PPIs or PPIs and H2 receptor antagonists were observed.

A hearing concerning the reimbursement conditions was conducted by the Norwegian Medicines Agency in the autumn of 2006 (11). The goal of the revision of the

conditions for reimbursement of drugs for the treatment of GORD was a more cost-effective prescribing. A yearly savings of up to 83 million NOK was estimated by changing the reimbursement conditions, making PPIs other than esomeprazole the preferred drugs.

The sales of PPIs in Norway have had a quintupled increase since 1996. Information on the PPI users in the general population is, however, limited.

4 MATERIAL AND METHODS

Data were retrieved from the databases NorDWD and NorPD. In addition, data relating to total consumption were collected from the Swedish and Danish wholesale databases for comparison purposes with the Norwegian data.

4.1 The NorDWD

The database contains data from the total sales of drugs with a marketing authorisation in Norway. The figures represent sales from wholesalers to pharmacies, hospitals and non-pharmacy outlets. In addition, the database contains sales of drugs without Market Authorisation (MA) and OTC drugs.

Data are reported monthly from the wholesalers to the Department of Pharmacoepidemiology, Division of Epidemiology, Norwegian Institute of Public Health. The reporting is under the pursuance of Norwegian law. A selection of data is published in the yearly publication, ”Drug Consumption in Norway” (12).

The material can be sorted according to the ATC classification system with Defined Daily Doses employed as units of quantitative measurement.

Sales within the ATC code A02BC *Proton pump inhibitors* were retrieved for the 10-year period, 1996 to 2006. The ATC/DDD version valid from January 2007, was used in the material.

Estimate of the number of DDD/1000 inhabitants/day
The sales data may be given as the number of DDDs/1000 inhabitants/day, which is calculated as follows:

$$\frac{\text{Total consumption measured in DDDs} \times 1000}{365 \times \text{numbers of inhabitants}}$$

This figure provides a rough estimation of a prevalence; i.e., the proportion of the population that may receive a certain drug treatment. An estimated drug consumption of 10 DDD/1000 inhabitants/day corresponds to a daily use of a drug by 1% of the population.

Estimate of sales in NOK
Costs are expressed in pharmacy retail price (AUP). The calculation of the pharmacy retail price was based on the invoiced pharmacy purchase price with the pharmacy maximum margin, including fees and VAT (25%) added.

Prices pr DDD
The total number of DDDs sold of each substance were calculated and divided by respective AUP. This provides a rough estimate of the price development over time.

Percent share of the total sale of the different tablet strengths
The total number of PPI tablets sold of each strength was retrieved. The percent share of the different tablet strengths was calculated from the total number of tablets sold.

4.2 Drug wholesale data from Denmark and Sweden

An estimate of the number of DDD/1000 inhabitants/day in Denmark and Sweden was retrieved. From Denmark, data on drug consumption are available from the official publication, "Lægemiddelstatistikk 2002-2006" (39). Swedish data were retrieved from the database of Apoteket AB (Andersson K, personal communication).

4.3 The NorPD

As of January 1, 2004 and in accordance with Norwegian law, all pharmacies are obliged to submit electronic data on all prescriptions to the Norwegian Institute of Public Health. NorPD, thus, includes all prescriptions dispensed to the total population of Norway (4.6 million).

The database contains information from prescription drugs dispensed to individual out-patients with, whether reimbursed or not. The patient's identity has been encrypted with each record containing a unique person identifier. This makes it possible to identify all prescriptions per individual, and to follow the individual over time.

The following data were collected from NorPD:

1) Drug user
   Patient's sex*, age* and place of residence
   Date of dispensing*
2) Drug*
   Brand name of drug, package size, number of packages
   ATC code
   DDD
   Price according to the prescriptions
3) Prescriber
   Prescriber's sex and age

4) Pharmacy
Pharmacy identifier

*) data used in this study

The following analyses were applied:

Prevalence of PPI use 2006
A one year prevalence of PPI use was calculated by identifying the number of individuals who had at least one PPI prescription dispensed during 2006, divided by the population as of January 1, 2006 as stated in the Statistics Norway (40).

Incidence of PPI use 2006
Individuals were defined as incident users if a PPI was dispensed in 2006 with no prescriptions dispensed in 2005 (wash out period).

Long-term users
One of the criteria for reimbursement is a need for long term-treatment which is defined as more than three months during a year. Long-term users will normally have PPIs dispensed three to four times throughout the year. In this study, long term users were defined as individuals having a PPI dispensed in 2005 and 2006. In Tables 7 and 8, an individual receiving both a self payment prescription and a reimbursement prescription, were counted in both groups. An individual receiving a prescription for more than one substance, was also counted for each of the substances.

Adherence to therapy
A proxy for adherence to therapy was calculated as the part of the year covered by a DDD of a PPI. The users were defined in three groups: Adherence > 90 DDDs, > 180 DDDs and individuals using >360 DDDs pr year. The adherence is given as a percentage of the total consumers of PPIs.

Indications for reimbursement
The code for reimbursement is recorded and this may, with some reservations, function as a proxy for diagnosis. § 9 point 41 is the code for PPI prescribed for endoscopically verified reflux esophagitis. In addition, PPIs may be prescribed as a prophylaxis and treatment of gastric ulcers induced by NSAIDs.

5 RESULTS

5.1 Results from the NorDWD

5.1.1 Development of the consumption of PPIs measured in DDD/1000 inhabitants/day

There has been a strong increase in the consumption of PPI measured in DDD/1000 inhabitant/day. In 2006 the total consumption was 27.1 DDD/1000 inhabitants/day. During the period 1996 to 2006 the consumption of PPIs has quintupled (Figure 1).

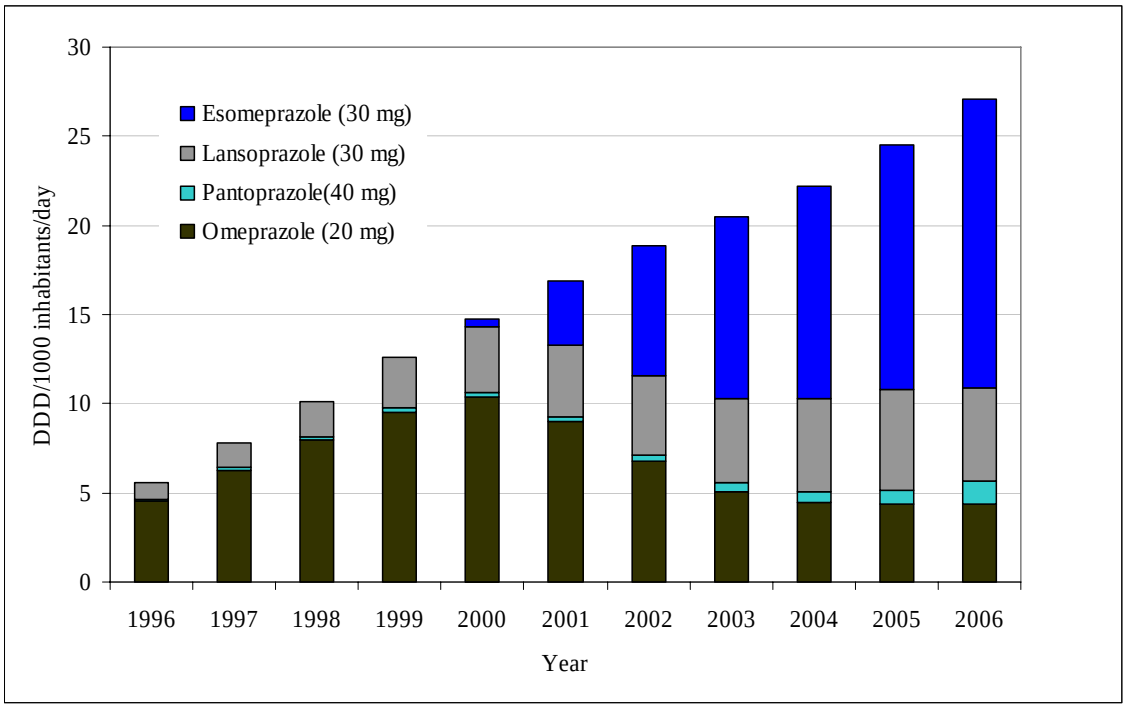

Figure 1: Consumption of PPI (ATC code A02BC) measured in DDD/1000 inhabitants/day - 1996 to 2006. Source: NorDWD, Norwegian Institute of Public Health

Esomeprazole was launched in the year 2000 and has steadily increased its share of the Norwegian market. In 2006, esomeprazole measured in DDDs, represented nearly 60% of the total market of PPIs. The market share of omeprazole has fallen during the same period, and was, in 2006, 16% of the total consumption. No major changes were observed for pantoprazole and lansoprazole.

5.1.2 Development of sales measured in NOK

In 2006 the total cost of PPI therapy was 453 million NOK. Measured in NOK, the sales of PPIs increased until 2002, when the omeprazole brand, Losec®, lost its patent protection and generic products were launched. In 2006 esomeprazole represented 77% (349 million NOK) of the total sales of PPIs measured in NOK (Figure 2).

In spite of the falling prices of omeprazole, the consequences of the increasing market share of the more expensive PPI, esomeprazole, are that the total costs have been relatively stable.

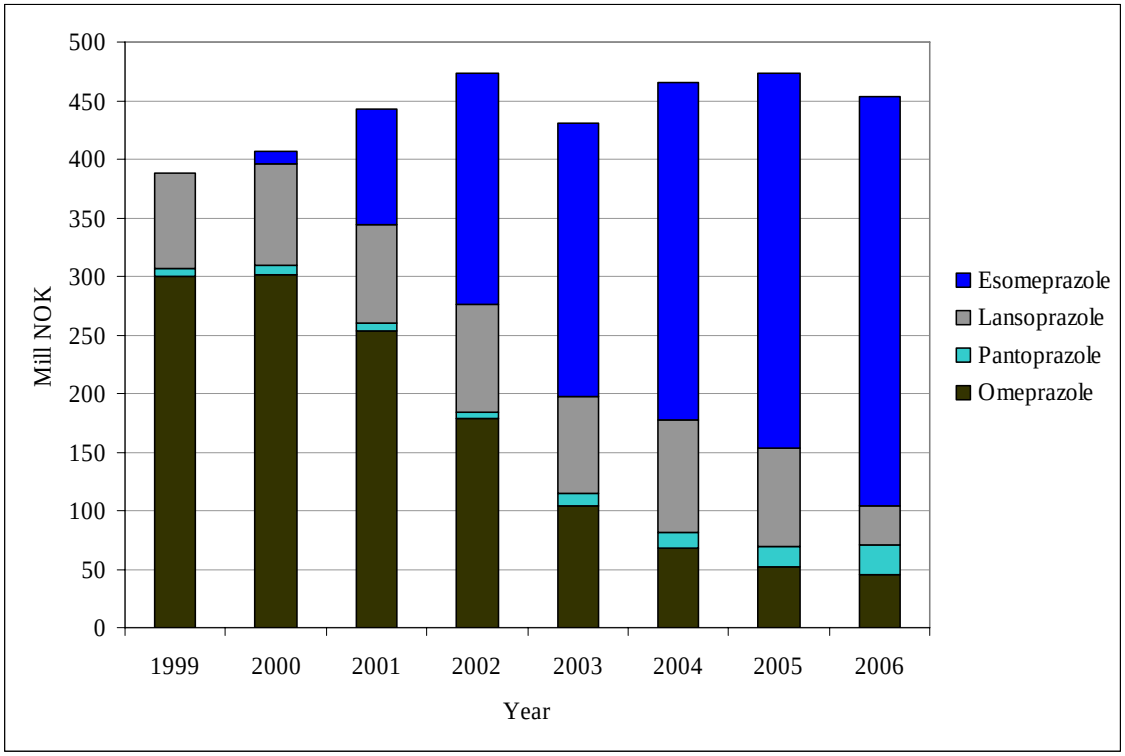

Figure 2: Sales of PPIs (ATC code A02BC) measured in million NOK (pharmacy retail price) 1999-2006. Source: NorDWD, Norwegian Institute of Public Health.

5.1.3 Development of prices per DDD

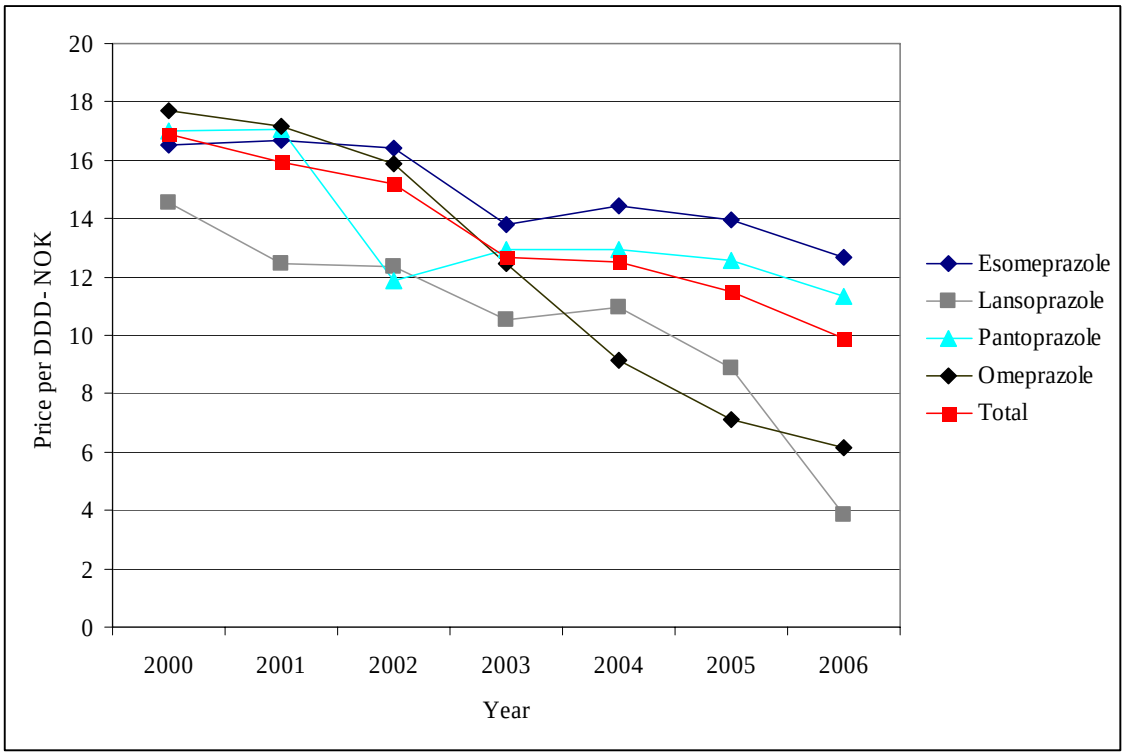

Figure 3: Prices per DDD for the different PPIs expressed in NOK – development 1999-2006. Source: NorDWD, Norwegian Institute of Public Health

When launched, new products with no specific therapeutic advantages are often priced somewhat cheaper than the reference products in the group. For example, this is the case with lansoprazole. This substance has been, and still is, one of the cheaper alternatives in the PPI group.

The generic competition has resulted in cheap generic alternatives for omeprazole and lansoprazole with esomeprazole, still having patent protection, at the top of the price curve. However, this PPI has also experienced a fall in prices, probably prompted by cheaper parallel imported products and also to somewhat compensate for the increasing price difference to omeprazole (Figure 3).

In 2006, if all PPI had been sold at the cost of the DDD price of lansoprazole, the theoretical maximum saving would be 275 million NOK, at the price of omeprazole, 172 million NOK.

5.1.4 Market share of different tablet strengths 2006

PPI	Strength	% market share (according to number of tablets)
Omeprazole	10 mg	7
	20 mg	93
Pantoprazole	20 mg	3
	40 mg	97
Lansoprazole	15 mg	10
	30 mg	90
Esomeprazole	20 mg	66
	40 mg	34

Table 3: The 2006 market share of different tablet strengths of the PPIs, % of total number of tablets sold of each substance. Source: NorDWD, Norwegian Institute of Public Health

Most tablets of omeprazole, pantoprazole and lansoprazole are sold in the highest strength. For esomeprazole, one third is sold in the tablet strength 40 mg (Table 3).

5.2 Development of the consumption of PPIs in Denmark and Sweden

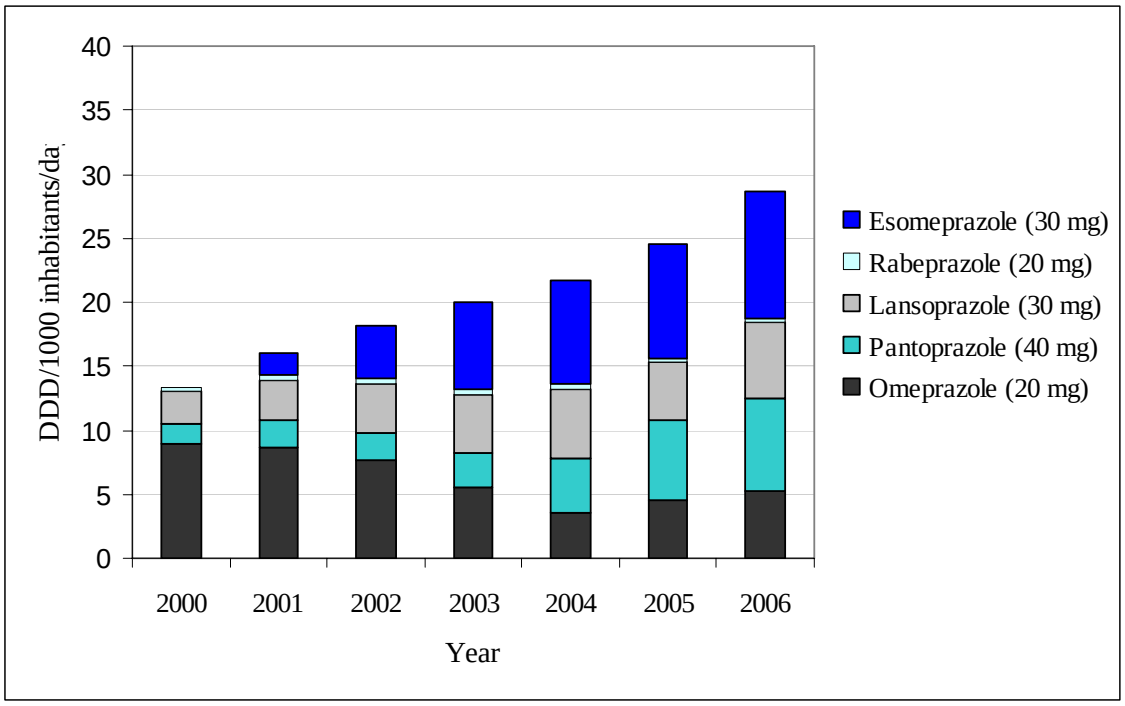

Figure 4: Consumption of PPI (ATC code A02BC) in Denmark measured in DDD/1000 inhabitants/day – 2000-2006 Source: Lægemiddelstatistikk 2001-2005 – Danmark (39) and the Internet (16).

In Denmark, there has also been an increasing consumption of PPIs. In 2006, the total consumption was 28.6 DDD/1000 inhabitants/day, an increase of 15% from the previous year. In 2006, esomeprazole represented 35% of the total consumption of PPIs. The share of all PPIs with generic alternatives is increasing (Figure 4).

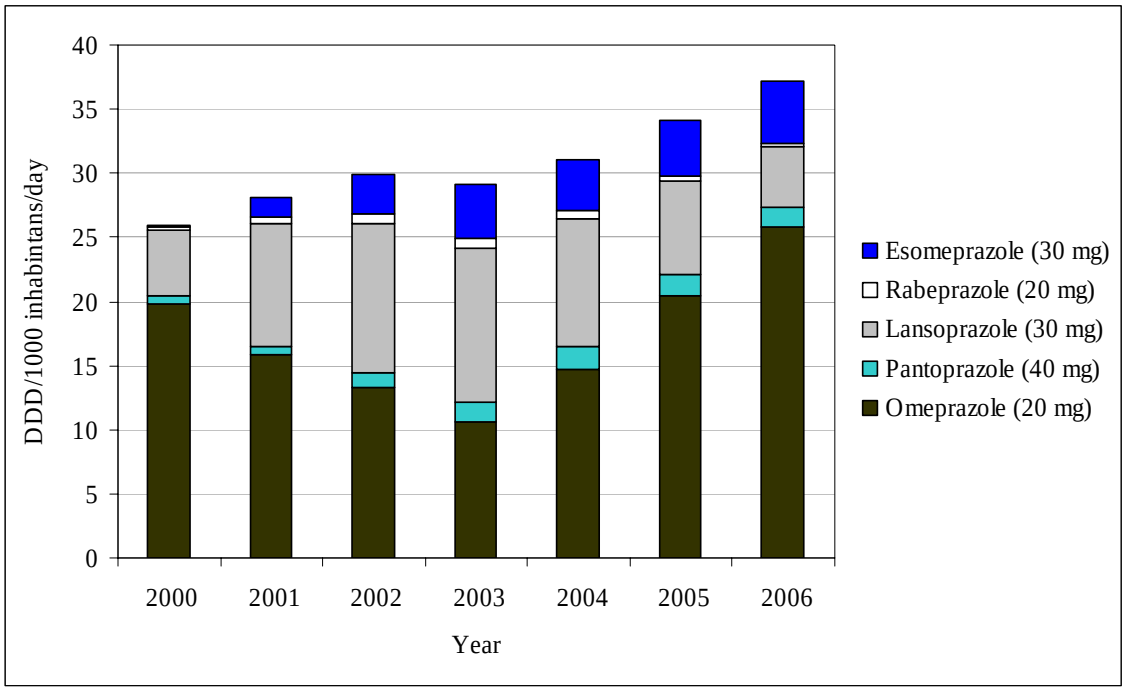

Figure 5: Consumption of PPI (ATC code A02BC) in Sweden measured in DDD/1000 inhabitants/day – 2000-2006. Source: Apoteket AB (Andersson K, personal communication).

In 2006, the total consumption in Sweden was 37.2 DDD/1000 inhabitants/day which was 37% higher than in Norway (Figure 5). Sweden has also seen an increasing consumption of PPIs; however, not as pronounced as in Norway and Denmark. Esomeprazole represented 13% of the total consumption of PPIs measured in DDD/1000 inhabitants/day, while omeprazole represented 69% of the consumption.

5.3 Results from the NorPD:

5.3.1 Prevalence of PPI use 2006

In 2006, the total one year prevalence of having at least one PPI dispensed was 44.3 per 1000 inhabitants (N= 205 622). The total pharmacy retail price for the sales of PPIs on prescriptions were 431 million NOK.

	Female			**Male**		
	Number of individuals	% of individuals per substance	Prevalence per 1000	Number of individuals	% of individuals per substance	Prevalence per 1000
Self payment prescriptions						
Omeprazole	3 235	9.0	1.4	2 367	8.6	1.0
Pantoprazole	2 610	7.3	1.1	2 172	7.9	0.9
Lansoprazole	4 336	12.1	1.9	3 788	13.7	1.6
Esomeprazole	25 714	71.6	11.0	19 339	69.9	8.4
	35 895	100		27 666	100	
Reimbursement prescriptions						
Omeprazole	11 511	13.9	4.9	10 366	13.4	4.5
Pantoprazole	4 182	5.0	1.8	4 204	5.4	1.8
Lansoprazole	14 978	18.0	6.4	15 344	19.8	6.7
Esomeprazole	52 373	63.1	22.4	47 503	61.4	20.6
	83 044	100		77 417	100	
Total number of individuals	**118 939**	**53.1**		**105 083**	**46.9**	

Table 4. The one year prevalence, according to sex, PPI-substance and prescription type (N= 224 022), of having at least one PPI prescription dispensed in 2006. Source: NorPD, Norwegian Institute of Public Health.

The number of individuals in Table 4 is somewhat greater than the overall number of individuals as some individuals might have had both types of prescriptions, as well as more than one PPI substance prescribed.

Individuals having reimbursement prescriptions represented 72% of the total number of individuals having a PPI prescription. As measured in DDDs, the reimbursement prescriptions represented 93% of the total costs and 94% of the consumption.

Esomeprazole was the most commonly prescribed PPI. Of the individuals having a self payment prescription 62%, received esomeprazole. Of the individuals having a reimbursement prescription 63% received esomeprazole. As measured in DDDs, esomeprazole constituted 76% of the reimbursement costs and 64% of the consumption.

	Female			**Male**	
Age groups	Number of individuals	Prevalence per 1000	Number of individuals	Prevalence per 1000	Total number of individuals
0 - 9	670	2.6	956	3.5	1 626
10 - 19	1 487	4.9	1 168	3.7	2 655
20 - 29	4 274	15.5	4 332	15.3	8 606
30 - 39	8 418	25.0	10 315	29.9	18 733
40 - 49	13 666	42.2	14 987	44.4	28 653
50 - 59	20 482	68.9	20 510	66.9	40 992
60 - 69	22 458	99.7	20 002	90.1	42 460
70 - 79	19 994	124.1	15 171	113.8	35 165
80 - 89	15 137	118.5	8 373	112.0	23 510
90 +	2 322	77.7	900	88.4	3 222
	108 908		96 714		205 622

Table 5: The number of individuals and prevalence according to age and sex (N= 205 622) of having at least one PPI dispensed in 2006. Source: NorPD, Norwegian Institute of Public Health.

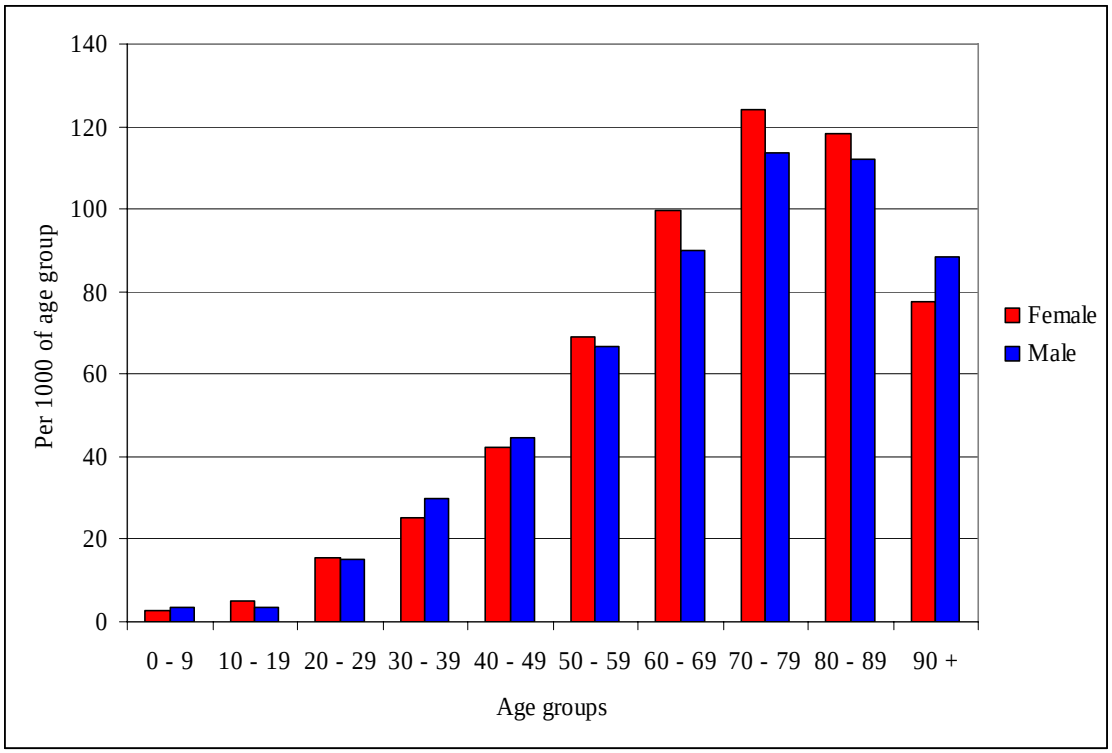

Figure 6: Ranking according to age and sex (N= 205 622) of the prevalence of having at least one PPI dispensed in 2006. Source: NorPD, Norwegian Institute of Public Health.

Prevalence increased with age with the highest prevalence, nearly 12% in the age group 70- 89 years. Women are in the majority in all the groups from 50 to 89 years and represented 108 908 (53%) of the total individuals (Table 5).

5.3.2 Incidence of PPI use 2006

In 2006, the overall incidence, new users having had no PPI dispensed in 2005, was 17.4 per 1000 inhabitants (N= 78 241). The number of incident users indicates that 38% of the prevalent users in 2006 were new PPI users.

	Female			**Male**		
	Number of new users	% of individuals per substance	Incidence per 1000	Number of new users	% of individuals per substance	Incidence per 1000
Self payment prescriptions						
Omeprazole	2 580	9.1	1.1	1 876	8.5	0.82
Pantoprazole	2 313	8.2	0.99	1 946	8.8	0.85
Lansoprazole	3 218	11.3	1.38	2 916	13.2	1.27
Esomeprazole	20 262	71.4	8.71	15 416	69.6	6.72
Sum	28 373	100.0		22 154	100.0	
Reimbursement prescriptions						
Omeprazole	2 449	10.8	1.05	2 157	9.9	0.94
Pantoprazole	2 221	9.8	0.95	2 313	10.6	1.01
Lansoprazole	2 821	12.5	1.21	2 923	13.4	1.28
Esomeprazole	15 102	66.8	6.57	14 385	66.1	6.35
Sum	22 593	100.0		21 778	100.0	
Total number of individuals	**50 966**	**53.7**		**43 932**	**46.3**	

Table 6. Incidence - new users having no PPI dispensed in 2005 – ranked according to sex, PPI-substance and prescription type (N= 94 898). Source: NorPD, Norwegian Institute of Public Health.

The number of individuals in Table 6 is greater than the overall number of individuals as some individuals might have had both types of prescriptions.

In approximately 7 of 10 cases, incident users received esomeprazole. When comparing prescription types or PPI prescribed, there are no major incidence differences between women and men. However, women had a 30% higher incidence of receiving a self-payment prescription for esomeprazole than men.

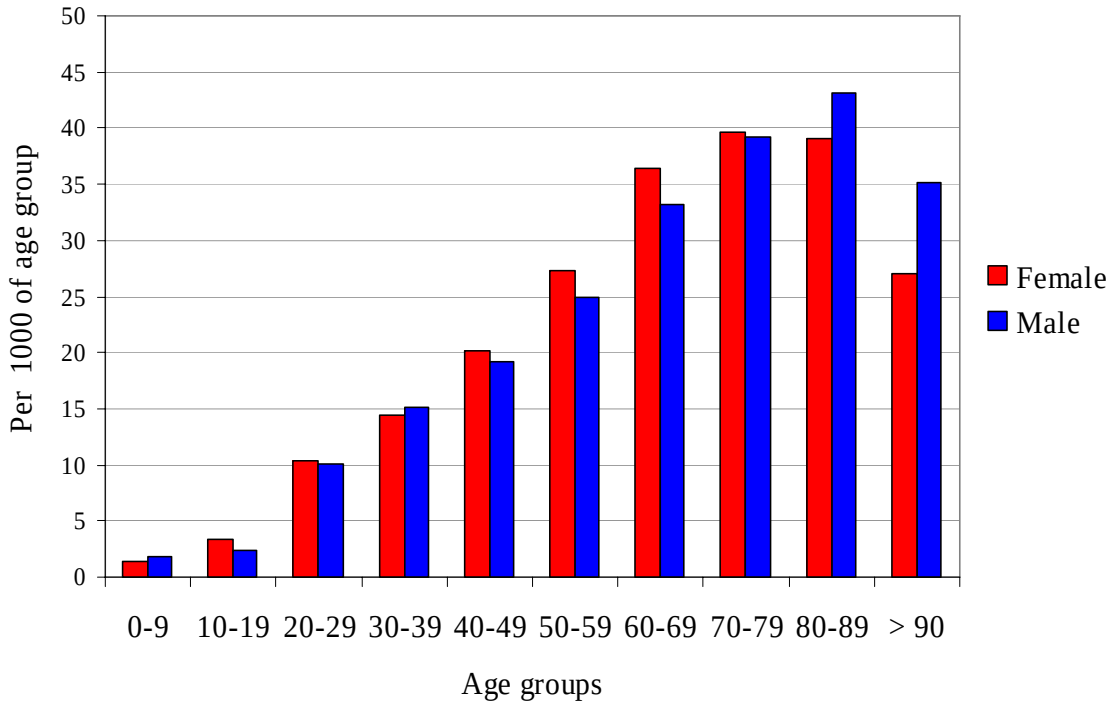

Figure 7: The incidence of a PPI dispensed for the first time in 2006 ranked according to age group and sex (N= 78 263). Source: NorPD, Norwegian Institute of Public Health.

The distribution of incidence over the age groups resembles the distribution of prevalence (Figure 7). Women represented 42 077 (54%) of the total number of individuals.

5.3.3 Long-term users

Of a total of 187 788 unique individuals having at least one PPI dispensed via a prescription in 2005, 127 381 (68%) also had a PPI dispensed in 2006.

Self-payment prescriptions
In 2005, the total number of individuals having at least one PPI dispensed via self-payment prescriptions was 52 634. Of these, 12 531 had a new dispensing in 2006 (i.e., 24% of the individuals had a new dispensing).

	Number of individuals with PPI prescription 2005	Number of these individuals with new PPI prescription 2006	% with new prescription 2006	% of 2005 DDDs prescribed to these individuals in 2006
Omeprazole	4 692	1 146	24.4	52.5
Pantoprazole	1 465	523	35.7	51.8
Lansoprazole	9 395	1 985	21.1	52.6
Esomeprazole	38 639	9 360	24.2	52.3
Sum	**54 191**	**13 014**		

Table 7. According to the different PPI substances, individuals having a PPI dispensed via a self-payment prescription in 2005 and continued in 2006. Source: NorPD, Norwegian Institute of Public Health.

Reimbursement prescriptions
In 2005, the total number of individuals having at least one PPI dispensed via reimbursement prescriptions was 144 466. Of these, 111 707 had a new dispensing in 2006 (i.e., 77% of the individuals had a new dispensing).

	Number of individuals with PPI prescription 2005	Number of these individuals with new PPI prescription 2006	% with new prescription 2006	% of 2005 DDDs prescribed to these individuals in 2006
Omeprazole	21 963	17 276	78.7	88.8
Pantoprazole	4 903	3 854	78.6	94.0
Lansoprazole	35 000	24 576	70.2	82.4
Esomeprazole	89 433	70 378	78.7	97.2
Sum	**151 299**	**116 084**		

Table 8. According to the different PPI substances, individuals having a PPI dispensed in 2005 via reimbursement prescription and continued in 2006. Source: NorPD, Norwegian Institute of Public Health.

The total number of individuals in Tables 7 and 8 is greater than the overall number of individuals as some individuals may have had both types of prescriptions, as well as more than one PPI substance prescribed.

5.3.4 Adherence to therapy (number of days covered by a DDD)

	Self payment prescriptions		**Reimbursement prescriptions**	
DDD groups	Number of PPI users	% of users with more than stated DDD	Number of PPI users	% of users with more than stated DDD
>90 DDD				
F	3 183	9.2	58 975	74.1
M	2 496	9.3	54 657	73.1
Sum	5 679	9.2	113 632	73.6
>180 DDD				
F	1 453	4.2	50 112	63.0
M	1 084	4.0	46 470	62.2
Sum	2 537	4.1	96 582	62.6
>360 DDD				
F	331	1.0	20 761	26.1
M	224	0.8	19 407	26.0
Sum	555	0.9	40 168	26.0

Table 9. The number of days covered by a DDD as a proxy for adherence to PPI therapy in 2006 ranked according to sex and prescription type: Self-payment prescription (N= 61 116) and reimbursement prescription (N= 154 355). Source: NorPD, Norwegian Institute of Public Health.

The number of days covered by a DDD, a proxy for adherence to PPI therapy, for individuals having PPI dispensed according to self-payment prescription was very low (Table 9). Of the users having PPIs dispensed on a reimbursement prescription, 63% had more than 180 DDDs dispensed in 2006.

5.3.5 Indications for reimbursement

Reimbursement indications (reimbursement reference code)	**Number of individuals**	**% of total**
Ref. code 41 - Verified reflux oesophagitis (GORD)	152 463	95.4
Ref. code 3 - Arthritis urica and similar diseases	630	0.5
Ref. code 17 - Polyarthritis chronica and morbus Bechterev	749	0.4
Ref. code 35 - Cox- and gonartritis.	245	0.2
Others	5 886	3.6
Sum		**100**

Table 10. Reimbursement reference codes for PPI prescribing in 2006 as stated on the prescriptions. Source: NorPD, Norwegian Institute of Public Health.

The dominating indication for reimbursement prescribing as stated on the prescriptions was a verified reflux oesophagitis. Other possible reimbursement possibilities (prevention and treatment of NSAID induced ulcers in connection with treatment for different rheumatologic conditions) were used to an insignificant extent (Table 10).

6 DISCUSSION

GORD and other gastric acid related disorders represent a considerable burden of disease in the population. GORD is one of the most common indications for reimbursement prescribing in Norway. In 2006 the PPI esomeprazole was the fourth most sold prescription-only drug according to NOK value. Esomeprazole represented 76% of the total reimbursement costs of PPIs for GORD.

The consumption of PPIs in Norway is characterized by a yearly increase of approximately 10% as measured by DDD/1000 inhabitants/day. The most expensive PPI available, esomeprazole, is the most common drug. In 2006, 7 of 10 new PPI users received esomeprazole. This PPI had a cost three times higher per DDD than the cheapest alternative, lansoprazole. Treatment persisted over a two-year period for 77% of patients receiving reimbursement prescriptions. Of the patients on PPI treatment, 63% had more than 180 DDDs dispensed annually.

Method discussion

Combining data from a wholesale based data register with individual based prescription data provides a good basis for a descriptive, epidemiological study of drug use. Both registers encompass the country as a whole. The information contained in these registers can be regarded as complete for the Norwegian population. However, both sources have their limitations.

Data delivered from wholesalers do not necessarily represent what is actually consumed. The premises on which the data are based have to be considered when interpreting and evaluating the data. However, these data are easily available for analysis. Used with the ATC/DDD methodology, wholesale data give an overview of the drug market and make it possible to identify drugs and groups of drugs where further research would be of benefit to the health of the population. The consumption is measured in DDD/1000 inhabitants/day, giving a rough estimate of a given prevalence. This unit makes it easy to follow-up drug consumption over a period of time.

Since the main purpose of the ATC/DDD system is to present drug utilization statistics, using DDD when comparing prices is regarded as a misuse of the system. For selected groups of drugs, however, prices per DDD can give an illustration of the price development.

Prescription data on an individual level provides a more accurate description of drug consumption and opens the possibility for extensive research on drug consumption. However, as for the wholesale data, they do not necessarily represent what is actually consumed by the patients. The NorPD also covers the entire population. Information regarding individual prescribing is limited to out-patients. Information on individual levels for patients in hospitals and institutions are not included. In the older age groups, especially in those over 80, a proportion of the individuals will be in institutions and homes for the elderly and thus not included in the statistics. Overall prevalence and incidence, especially in the elderly, will therefore be underestimated.

Diagnosis or diagnosis codes are registered in the NorPD. The indication for drug use and prescribed dosage are stated by the pharmacy on the label in free-text and are not yet available for research. The reimbursement code may, with reservations, function as a proxy for diagnosis.

The NorDWD

During the period 1996 to 2006, the sales of PPIs has quintupled. In 2006, the consumption was 27.1 DDD/1000 inhabitants/day, representing a value of 453 million NOK.

With the introduction of esomeprazole in 2000, this PPI has comprised an increasingly larger part of the market. In 2006, esomeprazole represented 77% (349 million NOK) of the costs of all PPIs, but only 60% of the sales measured in DDD/1000 inhabitants/day.

Parallel to the increasing sales of esomeprazole, the sales of the first PPI on the market, omeprazole, has decreased from 71% of the total market measured in DDD/1000 inhabitants/day in 2001 to 16% in 2006. This coincides with the loss of patent protection for omeprazole and the introduction of generic alternatives. For lansoprazole and pantoprazole, the consumption has changed only marginally over the last 5 years. The considerable decline in prices of omeprazole, pantoprazole and lansoprazole seem to have had no influence on the prescriber's choice of PPI. A shift to the prescribing of these PPIs would have had a considerable effect on the expenditure for PPIs. The theoretical saving is in the magnitude of 170-270 million NOK, calculated by using the cost pr DDD in 2006 of the cheapest PPIs.

More than 90% of omeprazole, pantoprazole and lansoprazole tablets are sold in strengths reflecting the DDD, 20 mg, 40 mg and 30 mg, respectively. For esomeprazole, two thirds of the tablets are sold as 20 mg and one third as 40 mg. The DDD for this PPI is 30 mg. Since the normal dosage of PPIs is one tablet daily according to the approved dosage recommendations, the DDDs seem to be representative of the prescribed daily doses of the PPIs.

The NorPD

In 2006, the overall prevalence of PPI use was 44.3 per 1000 inhabitants, with patients receiving self-payment prescriptions representing 28%. However, reimbursement prescribing represented 93% of the total costs in million NOK with 94% of the consumption in DDDs. This confirms that patients needing long-term therapy, or high doses receives to a large extent, reimbursement prescriptions.

More than 6 out of 10 prevalent users received esomeprazole. Women had a higher or equal prevalence of receiving a PPI prescription than men for all PPI substances and both prescriptions types, with the one exception being lansoprazole; reimbursement prescription.

The prevalence of having a PPI prescribed increased with age, with maximums of nearly 12% in the age groups 70-79 and 80-89 years. Patients in these age groups are

frequently exposed to polypharmacy. In a Danish study, the prevalence of polypharmacy increased with age. From the age of 70 years, two thirds of all the drug users were polypharmacy users which was defined as using five or more drugs (41). The high prevalence of PPI treatment in the elderly could indicate a use of PPIs in connection with acid-related gastric disorders as an adverse reaction to other drugs (e.g., NSAIDs). Prevalence in the elderly is underestimated since only prescriptions for open-care patients are included in the NorPD.

In 2006 the overall incidence (i.e., new users having had no PPI dispensed in 2005), was 17.4 per 1000 inhabitants with 7 of 10 incident users receiving esomeprazole. In 2006, 38% of the prevalent users were new PPI users.

The incidence of users receiving a first time self-payment prescription or reimbursement prescription is similar. The differences between sexes are small; however, women had a higher incidence of receiving a self-payment prescription than men and a 30% higher incidence of receiving the most expensive PPI alternative.

The age distribution of incidence resembles that of the prevalence; incidence is increasing with age. In the oldest age groups, information regarding individual prescribing does not include patients in hospitals or long-term care facilities; therefore incidence will be underestimated.

In this study, long-term use is defined as PPI users in 2005 continuing with therapy in 2006. Of the total number of PPI users having at least one PPI dispensed in 2005, 68% had a new prescription dispensed in 2006. Users receiving self-payment prescriptions constituted one fourth of the total individuals. Approximately 24% of the PPI users receiving a self-payment prescription in 2005 continued with a self-payment prescription in 2006, while 77% of the individuals receiving a reimbursement prescription in 2005 continued with a reimbursement prescription in 2006.The proportion of users continuing on PPI, constituted more then 90% of the 2005 DDDs re-prescribed. For nearly 8 of 10 users, use of PPIs according to imbursement prescription seemed to persist over a two-year period.

The proportion of the year covered by a DDD can be used as a rough indicator of adherence to PPI therapy. Users having PPI dispensed according to self-payment prescription had a very low adherence, illustrating that these are patients needing a PPI occasionally. Of the users, 63% having PPIs dispensed on a reimbursement prescription had more than 180 DDDs dispensed during 2006. This reflects a proportion having a chronically medium high to high consumption of PPIs, and includes the 26% of the users that had more than 360 DDDs dispensed in 2006.

Reimbursement prescriptions represented 93% of the total value of the PPIs prescribed in 2006. Verified GORD was nearly the sole criterion for reimbursement according to the prescriptions. Even though reimbursement is also granted for the prevention and healing of NSAIDs-related gastric ulcers. Prescribers applied this criterion to a very low extent. Through questionnaires completed by the general practitioners, a prescription study identified reasons for prescribing PPIs. In this sample, prescribing were associated

with other drugs (56.1%), gastroesophageal reflux disease (29.4%) and dyspepsia (11.4%). The rate of non-compliance with the marketing authorisation indication (GORD) was 46.3%, including 20.4% for inappropriate medical indications (42). It seems unlikely that reimbursement prescribing of PPIs in Norway reflects the real prevalence of verified GORD.

Drug wholesale data from Denmark and Sweden

The sales of PPIs are increasing also in Denmark and Sweden. The total consumption in Denmark, measured in DDD/1000 inhabitants/day, is at the same level as in Norway. In 2006, sales in Sweden were 37% higher than in Norway.

The consumption pattern of PPIs in Denmark and Sweden has had the opposite development when compared with the Norwegian. While esomeprazole is the dominant substance in Norway, Denmark has a balanced use of the four substances included in the PPI group with an increasing share of substances with generic alternatives. In Sweden in 2006, omeprazole represented 69% of the PPI sales measured in DDD/1000 inhabitants/day. The Swedish consumption development indicates that generic omeprazole products are prescribed to an increasing extent.

In Norway, the prescribers have increasingly preferred the newest, still patent-protected substance in the group, while the generic PPI alternatives are prescribed at a lower rate. According to the new reimbursement criteria, from February 1, 2007, esomeprazole is reserved for patients unable to use any of other PPI on the market (43). This will undoubtedly increase the market share of omeprazole and the other PPIs.

General discussion

In the initial treatment of erosive GORD, doses up to 40 mg per day of esomeprazole have demonstrated a better effect then the other PPIs (30). Of the sales of esomeprazole, 33% are in the high strength, 40 mg, indicating a considerable number of patients on high-dose therapy. Since esomeprazole is the S-enantiomer of omeprazole, 40 mg esomeprazole is assumed equivalent to 60-70 mg omeprazole (33;34). However, satisfactory equipotency studies of esomeprazole and omeprazole are not available. An American study was conducted to determine whether patients requiring doses greater than a single-dose PPI (i.e. high doses) for initial symptom resolution could be stepped-down to single-dose PPI and whether this decreased costs or adversely affected the quality of life. It was concluded that the majority of patients being asymptomatic after an initial treatment of greater-than-single-dose PPI might be stepped-down to a single-dose therapy without recurrence of reflux-type symptoms. The intervention decreased management costs without adversely affecting the quality of life (44). A study of primary care patients on PPI showed that a substantial proportion of the patients had indications not requiring long-term treatment using proton pump inhibitors. Half the patients used PPIs on-demand or intermittently (45). Also, in Norway, most of the PPI users probably have GORD to a milder degree or other gastric-acid related disorders. These patients could probably be treated with any of the PPIs in standard, recommended doses or with a lower maintenance dose.

The PPIs have few serious adverse effects in short-term follow-up studies and there are no consistent differences between the PPIs. The acid suppressing effect of PPIs are dosage-dependent; however it is difficult to determine the dosage for optimal symptomatic treatment in the individual patient (46). Patients may suffer from a short-term hypersecretion when treatment is discontinued. The fact that the adverse effects are few and the discontinuing of PPI therapy may be difficult, contributes together to a long-term or continuous use of PPIs.

This study demonstrates that a considerable part of the users have PPIs for at least two years. Consequences of long-term use of PPIs are continuously being discussed. Increased risk of esophageal and ventricular cancer has been postulated (46). A recent study from the Primary General Practice Research Database Care in UK showed an increased risk of hip fractures associated with persons older than 50 years using PPI for more than one year. The risk increased over time along with an increasing dosage (47). A recommendation from this study, quoted by the Norwegian Medicines Agency, is that patients needing therapy for more than one year, should preferably use the less potent H_2 -receptor blockers (48).

A descriptive pharmacoepidemiological study can not conclude on the rationality of PPI therapy in Norway. However, many authors suggest that there is an overuse of PPIs. A considerable proportion of the PPI users are suffering from mild GORD, non-ulcer dyspepsia and unspecific gastric disorders. It is possible to reduce the costs of PPI therapy by a shift to the prescribing of the generic alternatives. However, reduced costs alone are not a sufficient criterion for a more rational use of the PPIs.

Measures to increase the rational use of the PPIs are needed. More attention should be focused on correct usage, reduced dosages, the possibility of discontinuation of treatment and guidelines for such discontinuation. More research should be conducted on the co-prescribing of PPIs to polypharmacy patients.

7 CONCLUSIONS

The consumption of PPIs in Norway is increasing by approximately 10% per year, with esomeprazole as the most commonly used drug. In 2006, 7 out of 10 new patients received esomeprazole, with a three times higher cost per DDD than the cheapest alternative (lansoprazole). A shift in therapy to lansoprazole and omeprazole would create considerable savings for the reimbursement schemes.

For patients receiving reimbursement prescriptions, treatment persists over a two-year period for 77% of the patients, with 63% consuming more than 180 DDDs yearly. The prevalence of PPI use increased with age, having a maximum of nearly 12% in the age groups 70-79 and 80-89 years of age. These groups have a high risk of polypharmacy.

Confirmed GORD disease is the predominant criterion for reimbursement prescribing of PPIs. Other reimbursement possibilities were used at a very low extent.

The consumption patterns and levels of PPI in Norway, Denmark and Sweden are different. In Sweden, the level of consumption, measured in DDD/1000 inhabitants/day, in 2006 was 37% higher than in Norway with and the generic PPIs, especially omeprazole, dominating the market. In Denmark, the level of PPI consumption was comparable with that of Norway; however none of the PPIs were dominant market leaders.

There are indications of an overconsumption of PPIs. Few serious adverse effects and short-term hypersecretion upon discontinuation of PPI treatment may contribute to a high persistence of use. Even though the PPIs have been on the market for many years, negative effects associated with long-term use are being discussed and need to be further explored. Attention should be focused on the rational use of PPIs and not only on the reduction of costs.

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