Reservation notes against generic substitution - solely medical considerations?

An analysis of factors influencing the level of doctors' reservations against generic substitution for selected pharmaceuticals in Norwegian settings, 2006-2010.

Anna Stoinska-Schneider

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Institute of Health and Society

Department of Health Management and Health Economics

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Abstract

Background: The generic substitution scheme obliges pharmacies to offer patients the least expensive (usually generic) version of the prescribed medicine. In the presence of important medical reasons, prescribers can oppose substitution by making a note on the prescription. For reimbursable drugs with the doctor's reservation on the prescription, the patient's out-of-pocket payment remains the same as if the substitution did take place. The positive price difference is then covered by the National Insurance Scheme. When it is the patient who objects the substitution (patient's reservation), without the note from his/her doctor, it is the patient who has to pay the price difference him/herself. The level of doctors' reservations varies a lot across different areas of use and single substances. The average reservation rate for all substances is at the level of 5%, but for some preparations it can reach as high as 40%, which has its implications on the private and public pharmaceutical expenditure.

Objectives: To examine some of the non-medical reasons for variation in doctors' reservation levels. In particular the relationships between variables such as price difference between the original and generic alternatives, pharmacy chains, level of centrality, type of pharmaceutical and the corresponding level of doctors' reservations are being tested.

Methods: Descriptive statistics and binominal logistic regression were used to analyze an extensive dataset covering monthly records of sales, reservation levels and prices for selected 9 pharmaceutical substances dispensed from all Norwegian community pharmacies, aggregated on the level of municipalities and pharmacy chains, in 5 different periods. In addition a mini focus group with 6 general practitioners from Oslo area was also performed to obtain professional opinions about the hypotheses, as well as to capture observations and attitudes towards generic substitution and doctors' role in the scheme.

Results: The hypothesis about the influence of price difference between generic and brand name preparations on doctors' reservation levels remains unsupported. Type of pharmaceutical and centralization level proved to be significant and consistent as predictors of doctors' reservations. Pharmacy chain identity is to some extend important but unstable in time.

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Anna Stoinska-Schneider

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List of acronyms

ATC Anatomic Therapeutic Chemical classification

DDD Defined Daily Doses

EPJ Electronic Patient Journal

FHI Norwegian Institute for Public Health

GP General Practitioner

HELFO The Norwegian Health Economics Administration (Helseøkonomiforvaltningen)

NAV The Norwegian Labor and Welfare Organization

NICE The National Institute for Health and Clinical Excellence (UK)

NIS National Insurance Scheme

NOK Norwegian Kroner

NoMA Norwegian Medicines Agency

NorPD Norwegian Prescription Database

OTC Over-the-counter. Nonprescription drugs

POD Prescription-only drugs

PPIs Proton pump inhibitors

PPP Pharmacy Purchasing Price

PRP Pharmacy Retail Price

SSRIs Selective Serotonin Reuptake Inhibitors

1 INTRODUCTION

1.1 Background

Generic substitution at the Norwegian pharmacies was introduced in March 2001. The principle of the new regulation was to ensure a decrease in prices after the expiry of patents on original medicines, in order to contain the public pharmaceutical expenditures as well as those of the patients. After a decade in use, the scheme, together with the stepped-price system have been estimated to save the society about 2 billion Norwegian Kroner annually. Despite the undisputable success, generic substitution still faces some challenges, such as problems with correct use of the interchangeable medicines and some skepticism among patients (and some doctors).

The scheme obliges the pharmacies to offer patients alternative and less expensive preparations (at stepped-price level), which are copies of the original drugs, but can differ in name, taste, and external features from those prescribed by doctors. Despite these differences both original and generic preparations contain the same active substance, and pass the same requirements for quality, effectiveness and safety. Still, patients must always be informed whenever the substitution takes place.

In the presence of important medical reasons for which the patient has to be given the brand-name product, such as high risk of non-compliance or adverse reaction to particular inactive substance, the doctors can make a note on the prescription here called a reservation note (an objection against substitution), to ensure that the pharmacy will dispose the original preparation instead of any alternatives. For reimbursable drugs with the doctor's reservation on the prescription, the patient's out-of-pocket payment remains the same as if the substitution did take place. The positive price difference between the original and generic medicines is in this case covered by the National Insurance Scheme. It is important to emphasize that doctors cannot issue reservation notes based on prejudices, skepticism or beliefs of lower quality.

In situations when it is the patient who objects the substitution (patient's reservation), without the note from his/her doctor, it is the patient who has to pay the price difference him/herself. The level of doctors' reservations varies a lot across different areas of use and single substances. The average reservation rate across all substances is at the level of 5%, but for some preparations it can reach as high as 40% (for example, as in the case of an acid-modifying medicine, omeprazole). There are surely clinical reasons for doctors to write reservation notes, but are these medical motivations exclusive factors in every case?

1.2 Main objectives

The present study is an attempt on determining some of these non-medical reasons for variation in doctors' reservation levels. Statistical analyses of a dataset reporting sales, reservation, prices and other variables (discussed in details in Chapter 5) are used to test potential factors (predictors) and their influence on the doctors' reservation levels. In particular, the relationships between variables such as price difference between the original and generic alternatives, pharmacy chains, level of centrality (geographical location of dispensing pharmacy), type of pharmaceutical and the corresponding level of doctors' reservations are being tested.

1.3 The thesis' structure

In the first part of the thesis (Chapter 2) a thorough description of the pharmaceutical system in Norway, along with pricing, reimbursement and generic substitution regulations will be given. Chapter 3 provides basic information on the pharmaceuticals selected for the analyses as well as on their users. The following part (Chapter 4) introduces some theory on prescription decisions in general and generic substitution in particular and some previous studies on the subject. At the end of this chapter, the main hypotheses of this thesis are presented.

Chapter 5 presents the empirical part of the thesis: the methods used datasets, variables and statistical tools, while Chapter 6 contains reports on the results. The seventh and final Chapter contains conclusions, and discussion of the findings.

2. DESCRIPTION OF THE SYSTEM

2.1 Norwegian Pharmaceutical system

2.1.1 The Norwegian Medicines Agency

The Norwegian Medicines Agency (NoMA) is the national, regulatory authority for medicines and the pharmaceutical supply chain. The agency is subordinate to the Ministry of Health and Care Services, and responsible for supervising the production, trials and marketing of medicines as well as their classification, pricing and reimbursement. NoMA approves medicines and monitors their use, and ensures cost-efficient, effective and well-documented use of medicines.

2.1.2 Supply chain

All major international pharmaceutical companies are active on the Norwegian market. Their market share is varied and rather dispersed, without clear dominants. The biggest company (Pfizer AS) controls 11.2 % of the market [i], there are also ten pharmaceutical companies producing medicines in Norway. Nevertheless Norway imports most pharmaceuticals. The majority of the companies are represented by the Association of the Pharmaceutical Industry in Norway (LMI-*Legemiddelindustriforeningen*).

The distribution chain is constituted by (NoMA, 2008): private pharmacies (581), publicly-owned hospital pharmacies (33), small pharmacy outlets [1200-sell selected over – the – counter drugs (OTCs) and some prescription-only drugs (PODs) ordered from community pharmacies] and other retailers, which are only allowed to sell some OTCs (kiosks, supermarkets, convenience stores, petrol stations).

The biggest retail channel (private pharmacies) is dominated by three pharmacy chains, which are vertically integrated with their own full-range wholesalers and control 98% of the market[i]. The three pharmacy chains together with their market shares are presented in the table below.

Table 1. Distribution structure on the Norwegian Pharmaceutical market

Pharmacy chain	Owner	Wholesaler	Market share
Vitus / Ditt apotek	Celesio AG (Germany)	NMD (Norsk Medisinaldepot) Grossisthandel AS	47.6 %
Apotek 1	Tamro OY (Finland) Phoenix (Germany)	Apokjeden Distribusjon AS	28.9 %
Alliance / Boots	Alliance Boots Ltd. (UK)	Alliance Healthcare Norge AS	23.5 %

Source: Based on data from Apotekforeningen[ii] and LMI[i]

In addition, NMD supplies also hospital pharmacies.

The pharmacies also have their trade organization – the Norwegian Pharmacy Association (*Apotekforeningen*).

2.2 Pricing of pharmaceuticals in Norway

The market for pharmaceuticals is generally characterized by low price elasticity of demand (broadly speaking, people want the medication they need but not more), and consequently high market power on the supply side. This creates a substantial producer surplus and a very unfavorable situation for the consumers. Norwegian authorities have introduced an extensive price regulation system to counteract high prices driving the health expenditures up, as well as to ensure equal access to pharmaceuticals for anyone in need of them, regardless of their economical situation.

The Norwegian Medicines Agency (NoMA) is in charge of pricing individual pharmaceuticals by establishing a maximum pharmacy purchasing price (PPP). This regulation refers to all prescription-only medicines (POM) which are to be launched at the Norwegian market. Prices of over-the-counter (OTC) medicines are subject of the free market price competition. The PPP set by NoMA is generally based on reference prices in nine Western European countries, which include: Sweden, Denmark, Finland, UK, France, Germany, the Netherlands, Austria, and Belgium. PPP is the average of the three lowest prices. The international price referencing system has been in use since July 2002 (NoMA/PPRI, 2008). The selection of the reference countries is thought to be the most comparable to Norway.

2.2.1 Pharmacy margin

Pharmacy maximal margin rates are regulated only in case of prescription drugs and are currently at following levels [iii]: 7% of the first 200 NOK of (Pharmacy Purchasing Price) PPP-AIP and 4% of the remaining amount. In addition, there is a nominal margin of 22 NOK per package. A/B preparations (medicines containing narcotic or/and psychotropic substances) are subjects to the further 10 NOK of nominal margin per package. Table 2 presents the principles of margin regulation.

PPP in NOK	% Margin	Nominal margin per package	Addition per A/B preparation sold
0 – 200	7	22 NOK	10 NOK
> 200	4		

Table 2. Maximal pharmacy margin calculation for prescription drugs in Norway

The system allows for transparency and predictability of part of pharmacies' income related to sales of the prescription drugs. For example the maximal margin for a medicine with PPP = 400 NOK will be:

Max Pharmacy Margin = (200 x 0,07) + (200 x 0,04) + 22 = 44 NOK

In reality due to the strong vertical integration of the Norwegian pharmacy chains, the pharmacies are virtually their own wholesalers. And since the maximum margin regards only the pharmacy margins, the effective margin can be often even greater (Aarseth, 2001).

According to the study by Brekke et al. (2010b), the average effective margin for prescription pharmaceuticals in Norway is approximately 18%. The margins in the study were calculated in the following way:

M = (PRP-PPP) / PRP, where

M = Pharmacy percentage margin, PRP = average Pharmacy Retail Price, PPP = average Pharmacy Purchase Price

Section 2.4.4 contains further discussion on pharmacy margins and their implications for pharmacies' incentives to promote generic substitution.

2.3 Reimbursement regulation

2.3.1 General reimbursement regulations

The Norwegian health care system has been developed in consistency with the general welfare policy present in Norway since the end of World War II. The principal of equality of access to health and social services regardless of economic situation or geographical location has been the fundamental concept of this development. Health care as well as other state-provided services are financed through compulsory and universal tax-based National Insurance System (NIS). There exists also a system of patients' co-payments for out-patient care and reimbursed pharmaceuticals (the co-payment is 38 per cent). However the co-payments are applicable up to the determined upper-ceiling, which in 2011 has been set at 1 880 NOK[iv] . After reaching this amount in co-payments, patients are relieved from payments for the rest of the calendar year and their medical expenses are fully covered by the NIS. According to OECD Health Data for 2008 [v], total expenditure on health was 8.5% of the Norwegian GDP (out of which 7.6% was attributed to pharmaceutical expenditure). Public expenditure accounted for as much as 84.2% of the total sum and 70% of the pharmaceutical expenditure.

The NIS grants patients suffering from chronic and severe conditions the right to reimbursement of drug expenses. The treatment has to last for at least three months during a year to qualify for the scheme. The treatment must also fulfill criteria for cost-effectiveness. The NoMA publishes monthly the full list of pharmaceuticals which are eligible for reimbursement.

2.3.2 Preferred pharmaceutical model

"Preferred medicine" (called also a "first-choice'" or a "drug of choice" scheme) is a programme for reimbursable pharmaceuticals indicating products which are the most cost-effective within a group of medicines for certain conditions. The regulation is applied for drugs with equivalent therapeutic effect when there are significant price-differences. The system has been introduced by the NoMA to ensure promotion of use of the most cost-effective medicines and thus improvement of cost containment. The prescriber is obliged to prescribe the first-choice alternative. However in presence of serious medical reasons against the "preferred medicine", the scheme ensures that the patient can have the individually best treatment reimbursed. One of the first groups of medicines covered by the scheme was lipid-modifying agents, or cholesterol-lowering drugs (statins). Since June 2005, the prescribers are obliged to prescribe generic simvastatin to all new statin users, as well as switch their "old patients" using other statins to using simvastatin within transitional period of one year. Prescribing of other statins would continue for patients who cannot replace them with simvastatin for serious medical considerations. This reform proved to be very successful for the public budget, even though the number of statins users increases rapidly in Norway. According to the study by Sakshaug et al.(2007), who analyzed statin prescription in 13-month period before and following the introduction of the scheme, the proportion of new statin users prescribed simvastatin went up from 48% to 92%, resulting in decreased expenditure despite increase in prevalence of statin use. The study also found that nearly 40% of users of the more costly alternative atorvastatin, switched to simvastatin within one year period following the new regulation.

2.4 Generic substitution

2.4.1 Generic medicines

According to the European Medicines Agency (EMEA/CHMP: 2011) a generic medicine is defined as a product that represents:

- the same qualitative and quantitative composition in active substance(s) as the reference product,
- the same pharmaceutical form as the reference medicinal product,
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Generic medicines are generally copies of the original drugs that are no longer protected by patents. They contain the same active ingredient, though their composition may not be identical with the original. The incorporation of inactive ingredients which are different from the original formulation can make generics very different in appearance, with different colors, sizes and shapes from those of the originals. Still, the generic products must meet the same quality and safety standards as their branded counterparts. However, unlike the new original drugs, their generic followers are not required to go through complex, time- and resource-consuming clinical trials of efficacy and safety, but they need to positively pass the bioequivalence trials. The manufacturers of the brand name preparation naturally use their privileged position of an exclusive seller in the patent period setting the prices high, trying to recover high costs and risks associated with research and development of new pharmaceuticals, as well as simply maximize their profit. In the post-patent period they often maintain the high prices (at least for some time), exploiting the drug's strong identity and habits among prescribers and users (more on this in Chapter 4). It comes as no surprise that the generics are usually much less expensive than their original counterparts, as that is their chance to compete with the well-established original products.

"Bioavailability" is defined as the amount of the active agent that finally reaches the site of action. It is fundamental when it comes to the effectiveness and tolerability of a pharmaceutical.

Another central concept is bioequivalence. Two medicines are considered bioequivalent if they contain the same active substance and they have been tested to be of the same strength and finally they evoke the same effect in patients within the same time period. According to Birkett (2003), two products can be called bioequivalent if their bioavailability is similar enough to cause an effect of equal efficacy and safety.

The EMEA (EMEA/CPMP: 2001) extends this definition stating that a generic medicine's bioavailability has to lie between 80% and 125% of the original branded medicine. The EMEA emphasizes potential consequences of this interval. Patients, who are being often switched between different generic medicines, could receive a medicine with 125% bioavailability on one occasion, and 80% on the next. This would mean a 36% loss in bioavailability. If the patient were switched back to the 125% bioavailability medicine, they would experience a 45% increase in bioavailability. This change can impact on the control of the disease for the patient (EMEA/CPMP: 2001). Potential results of automatic generic substitution systems will be discussed further in chapter 4 of this thesis

2.4.2 Substitution scheme

All new pharmaceuticals entering the Norwegian market have to be registered, approved, and priced by the Norwegian Medicines Agency. The NoMA also creates a substitution list which includes interchangeable medicines. Pharmaceuticals must be approved as equivalent and interchangeable to be classified within the same substitution group. In practice, they are either generic versions of the original medicine or products coming from parallel import, i.e. virtually the same products as the branded ones already marketed in Norway, produced by the same manufacturer, but imported from a country where their price is lower. The substitution list is revised, updated and published by the NoMA on a monthly basis.

In 2001 the New Pharmacy Act was introduced, giving the pharmacies the right to apply substitutions between equivalent drugs within the same substitution group (§6-6)[vi] when dispensing prescription medicines. The scheme intends to increase price competition as well as reduce drug expenditures for both patients and the National Insurance System.

Presently, the pharmacies dispensing medicines are obliged to inform patients about the possibility of switching the prescribed drugs to the least expensive alternative within one

substitution group. Thus regardless of the prescribed trade name of a specific drug, a patient will be advised about the cheapest option, usually the generic one, containing the same active substance of the same form and strength. Patients can reject the substitution. However, they will have to bear the positive price difference between the generic alternative and the original medicine themselves. Also in case of reimbursed drugs the patient will have to bear the price difference. This price difference will not count as part of the 1880 NOK which is the upper-ceiling for co-payments in NIS. In the presence of important medical reasons to why a patient has to use the branded name medicine, the prescriber can reserve against generic substitution by making a note on the prescription. These important clinical reasons can include the patient's allergy to some of the inactive ingredients of generics, observed side-effects as well as significant risk of inappropriate use by patients used to using brand-name medications and confused by different appearance of the generic drugs (lack of compliance). In case of reservation against generic substitution is made by the prescriber, the difference in price is covered by the NIS. Effectively, the patients' out-of-pocket contribution remains unchanged.

2.4.3 Stepped-price model

When the patent protection period ends, and the original medicine is exposed to generic competition, the wholesalers' power to negotiate lower prices with the manufacturers increases. Sometimes they are able to acquire decreased prices also for the branded name pharmaceuticals. The stepped-price model was introduced in Norway in January 2005 to ensure that both patients and the NIS also benefit from this surplus created on the demand side. The new system forces the prices down. Because of the lack of price-sensitivity on the demand side, a price reduction to this extent would not take place without regulation. Without a system for price reduction, the distribution chain would benefit from lower purchasing prices due to generic competition. The retail prices however, would not be reduced to the same degree.

In the stepped price model prices are being gradually reduced by predefined rates. The system has been modified twice since its introduction; the last modification was implemented in January 2008. The degree of price reduction is dependent on annual sales turnover of a particular medicine. Stepped price is the maximum price reimbursed by the NIS expressed as a fraction of the maximum retail price (PRP) of the original preparation at the end of the patent protection period. It also applies to non-reimbursed prescription medicines. For

reimbursable drugs the stepped price is also sometimes referred to as the reimbursed price. The principles of the model are presented in the Table 3

Table 3 The stepped price model. Source: NoMA. Percentage figures represent price reductions in relation to the original maximum PRP

Sales PRP, 12 months before generic competition		**≤ 100 million NOK**	**>100 million NOK**	
	Time of price-cut			
1st step	Start of generic competition	30 %	30 %	
2nd step	6 Months after generic competition	55 %	75 %	
Sales PRP, ≥ 12 months after 2nd step		**>15 million NOK and ≤ 30 million NOK**	**>30 million NOK And < 100 million NOK**	**>100 million NOK**
	Time of price-cut			
3rd step	≥ 12 months after 2nd step	65 %	80 %	85 %

PRP=Pharmaceutical Retail Price

An empirical example of how the system works is simulated and presented in Table 4.

Table 4. Example of price calculation for a pharmaceutical with initial price of 1000 NOK and with annual sales for over 100 mln NOK, exposed to generic competition and subject to the stepped-price regulation.

	PRP (max retail price)	Reimbursment by NIS	Patient's co-payment*	Additional payment for patients rejecting generic substitution**	Patient's usual co-payment + the additional payment
Original preparation before the end of the patent period	1000	620	380	0	380+0=380
Stepped price with 30% price reduction	700	434	266	300	266+300=566
Stepped price with 75% price reduction	250	155	95	750	95+750=845
Stepped price with 85% price reduction	150	93	57	850	57+850=907

*Patient's co- payment is presently 38% of the PRP. Not applicable once the ceiling of total annual contribution 1880 NOK is reached. **Given that the price of brand name product remains unchanged

The pharmacies are obliged to have at least one preparation within each substitution group available at the stepped price. The stepped price does not depend on the purchasing prices of the wholesaler or the pharmacy. The construction of the scheme therefore encourages them to lower their purchasing prices. Since the reimbursed price is virtually fixed after one year, the whole supply chain's actors from the manufacturers to the pharmacies have strong incentives to minimize their costs and thus maximize their profits.

2.4.4 Why generic substitution?

Since 2005, the generic market share in Norway has been relatively stable and accounted for approximately 46% of the volume expressed in DDD (defined daily doses) and about 64% of the sales measured in PPP (Pharmacy Purchasing Price). [i]

Norwegian public authorities actively promote generic substitution for cost-containment reasons. According to the NoMA[vii] about 2 billion NOK are saved every year due to the generic substitution and the stepped-price system. Approximately 75% of this sum benefits the National Insurance budget while 25% benefits the patients.

The pharmacies also play a crucial role in the generic substitution scheme. Generally, due to the transparency and simplicity of the stepped price system, the economical outcomes are relatively predictable for all supply chain parties. The time and effort that the dispensing pharmacies spend on convincing patients to generic alternatives can influence generic sales and thus total pharmaceutical expenditures. Therefore they must be economically motivated to dispense generic drugs. The strong vertical integration existing between Norwegian pharmacies and wholesalers increase their power in negotiating lower prices with the manufactures. The pharmacies and wholesalers are allowed to keep the surplus between the stepped-price and their real purchase price. This translates directly into higher margins for the pharmacies giving them financial incentives for promotion of the generic substitution.
Brekke and his colleagues in their empirical study (Brekke et al. 2010a), analyzed the impact of pharmacy margins on the pharmacies' incentives for promotion of generic products in Norwegian settings. They compared ex-manufacturer prices with retail prices and observed that the pharmacies have substantially higher margins on generics than original drugs measured either as percentage margins or absolute margins. They also found a strong association between brand-name and generic margins and their market shares. The pharmacies are inclined to expend more effort in promoting generics when their margins are high relative to the brand-name products. This incentive is also increasing the lower the generic co-payment becomes relative to the brand name co-payment. In addition, the researchers concluded that a regressive mark-up scheme, that provides lower absolute margins on higher priced drugs (original drugs), will provide pharmacies with incentives to spend efforts on convincing patients to cheaper generic drugs.

Last but not least, generic substitution gives individual medicine users the possibility of lowering the financial burden of pharmaceutical therapies, achieving the same health outcomes.

3. INFORMATION ON THE SELECTED PHARMACEUTICALS AND THEIR USERS

Nine different substances among three ATC (Anatomical Therapeutic Chemical) groups have been selected for this analysis.

Table 5. Substances selected for the analysis

ATC code	Active agent	Class	Main indication
A02BC01	omeprazole	Proton pump inhibitors	Peptic ulcer/GERD
A02BC02	pantoprazole	Proton pump inhibitors	Peptic ulcer/GERD
A02BC03	lansoprazole	Proton pump inhibitors	Peptic ulcer/GERD
A02BA02	ranitidine	H2-receptor antagonists	Peptic ulcer/GERD
C10AA01	simvastatin	HMG CoA reductase	High cholesterol level
C10AA03	pravastatin	HMG CoA reductase	High cholesterol level
N06AB04	citalopram	selective serotonin reuptake inhibitors	Major depression
N06AB05	paroxetine	selective serotonin reuptake inhibitors	Major depression
N06AB10	escitalopram	selective serotonin reuptake inhibitors	Major depression

The sections below present general descriptions of the selected pharmaceutical together with their prevalence of use in Norway in the past few years and some demographic features of their users.

3.1 Statins

Cholesterol is a vital component of the cell membranes as well as bile acids, steroid hormones, and fat-soluble vitamins including Vitamin A, Vitamin D, Vitamin E, and Vitamin K. It is critical to the normal function of every cell in the body. However, the elevated level of cholesterol in the blood serum contributes to the development of atherosclerosis causing chest pain and becoming a major risk factor for cardio-vascular diseases (CVD), including heart attacks and stroke.

Statins are a class of drugs used for preventing and treating atherosclerosis that lower the level of cholesterol in the blood by reducing the production of cholesterol by the liver. Statins block

the enzyme in the liver that is responsible for making cholesterol. This enzyme is called hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Scientifically, statins are referred to as HMG-CoA reductase inhibitors. By reducing the production of cholesterol, statins are able to slow the accumulation of lipids in artery walls (plaques) and occasionally can reduce the size of plaques that already exist. In addition, through mechanisms that are not well understood, statins may also stabilize plaques and make them less prone to rupturing and promoting the development of clots (Medicine net [xii]). The crucial role of cholesterol in atherosclerosis is widely accepted by scientists. In addition to lowering cholesterol levels, statins also reduce inflammation, which could be another mechanism by which statins beneficially affect atherosclerosis. This reduction of inflammation does not depend on statins' ability to reduce cholesterol. Furthermore, these anti-inflammatory effects can be seen as early as two weeks after starting statins. The statins' indication area is therefore broadening. Still, most patients are placed on statins because of high levels of cholesterol. Though reduction of cholesterol is important, heart disease is complex and not always high cholesterol alone contributes to its development. Thirty-five percent of individuals who develop heart attacks do not have high blood cholesterol levels, yet most of them have atherosclerosis.

Statin use is in general safe and well tolerated in all categories of patients, including the elderly at risk. Serious side effects such as rhabdomyolysis (muscule fiber break down and enter the bloodstream) or severe liver damage are very rare but have been reported. Mild side effects may be managed by reducing statin dose or switching to another type of statin. However, sometimes discontinuation of the statin may be necessary.

Concluding, because of their efficiency, few contraindications and general safety, statins are expected to be increasingly used in the prevention and treatment of cardiovascular disease. Given the very high social and economic burden of cardiovascular diseases in most countries, it is not surprising why statins are attracting lots of attention from practitioners, patients, as well as policy makers.

Also in Norway the use of statins has been growing steadily in the recent years, becoming the second group of pharmaceuticals (measured in DDDs), among the most used [i] . In fact, measured in DDDs, the sale of statins in Norway is higher than in most other European countries.[xiii] The increase in number of DDDs does not reflect the increase in number of users,

since the prescribed daily dose has increased over time. As described in the study by Sakshaug et al.(2007), the introduction of new price and reimbursement regulations for the statins have resulted in reduced cost in the latest 5 year period, despite the increase measured in DDDs. When simvastatin was made the drug of choice in June 2005, many users had to be switched from more costly alternatives to simvastatin.

For the present analysis we have chosen two popular substances among statins: simvastatin (statin with most users and 5th most used medicine in Norway) and pravastatin. Table 6 and chart 1 presented below show the specification and number of users of the two substances and its development over the past few years.

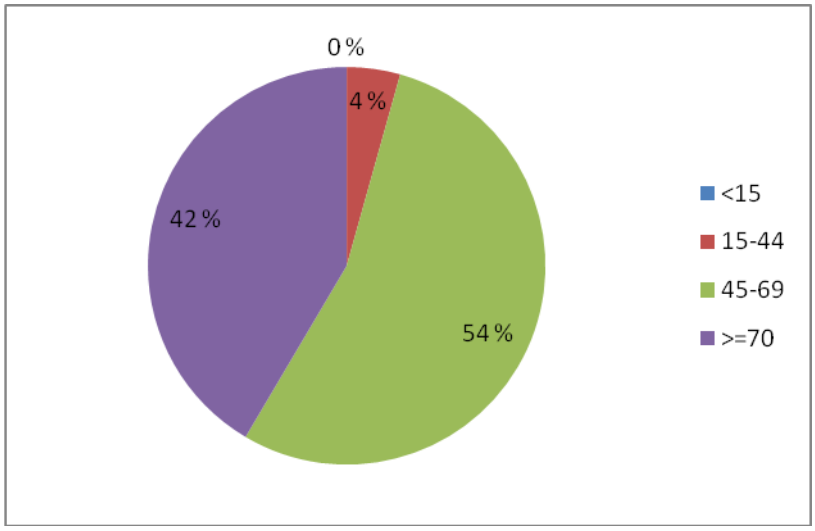
Table 6. Statins – number of users per substance and year.

ATC level	Active agent	Class	Name of the original product	Number of users			
				2006	2007	2008	2009
C10AA01	simvastatin	HMG CoA reductase	Zocor	254955	321025	348044	356617
C10AA03	pravastatin	HMG CoA reductase	Pravachol	28113	24230	23056	22324
TOTAL				283068	345255	371100	378941

Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009

One of the many common risk factors for arthrosclerosis and CVDs is age. Men over 45 years and women over 55 years of age are considered to be in a higher risk of developing serious CVDs. This is also reflected in the age interval for patients on statin therapy. The absolute majority of statin users are 45 years and over. See Chart 1 for age distribution for users of simvastatin and pravastatin in Norway.

Chart 1. Users of the selected statins in Norway by age. Data from 2009



Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009

3.2 Acid-suppressing drugs

Acid-suppressing medications (ATC: A02B) used mainly in therapies for peptic ulcer and gastroesophageal reflux disease (GERD) chosen for this study belong to two sub-groups: Proton pump inhibitors (PPI) and histamine H2 antagonists (blockers). List of the selected acid-suppressants is presented in the table 7.

Both PPIs and H2 blockers suppress gastric acid secretion, but at different stages of production. While histamine blockers block one of the first stimuli for acid production, proton pump inhibitors block the final step in the pathway of acid secretion in the stomach, resulting in greater suppression of acid. PPIs block the enzyme in the wall of the stomach that produces acid, H2 blockers work by blocking the histamine receptors in acid producing cells in the stomach. PPIs have a delayed onset of action, while H2 Blockers begin working within an hour. PPIs work for a longer period of time; most up to 24 hours and the effects may last up to three days. H2 Blockers, however, usually only work up to 12 hours[xii]. Despite these differences both groups of drugs reduce level of acid preventing formation of ulcers, and allow any ulcers that exist in the esophagus, stomach, and duodenum to heal. Apart from peptic ulcers the acid suppressants are used in gastro-esophageal reflux disease (GERD),

Zollinger-Ellison syndrome and elimination of helicobacter pylori (in combination with antibiotics).

Table 7. Acid suppressing medications - number of users per substance and year.

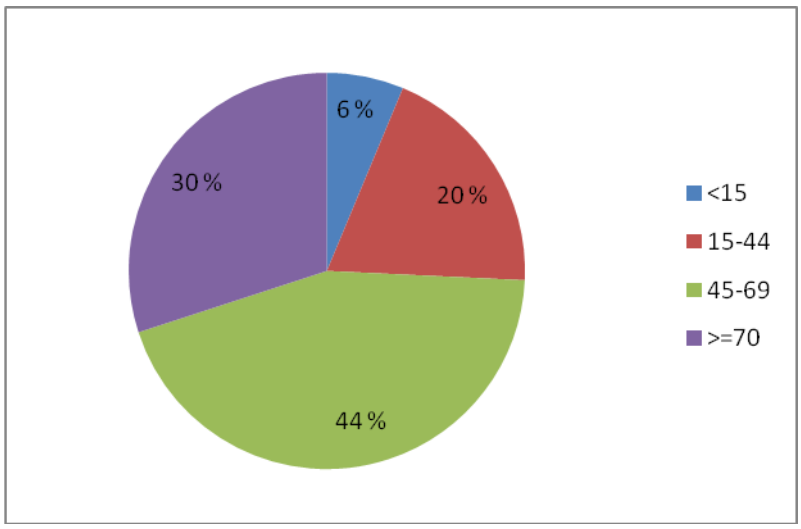
ATC level	Active agent	Class	Name of the original product	Number of users in Norway			
				2006	2007	2008	2009
A02BC01	omeprazole	PPI	Losec	27013	40043	44878	46831
A02BC02	pantoprazole	PPI	Somac	12691	57061	74962	85127
A02BC03	lansoprazole	PPI	Prevacid*	37108	48558	50409	49988
A02BA02	ranitidine	H2-receptor antagonists	Zantac	44649	50383	55440	55433
TOTAL				121461	196045	225689	237379

*Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009** Original unavailable on the market

Proton pump inhibitors are very similar in action and there is no evidence that one is more effective than another. They differ in how they are broken-down by the liver and their drug interactions. The effects of some PPIs may last longer and they, therefore, may be taken less frequently. For the present analysis we have chosen three popular PPI: omeprazole, pantoprazole and lansoprazole as well as the very popular H2 blocker: ranitidine. Ranitidine, omeprazole, and pantoprazole are also sold as OTC drugs in Norway. The proton pump inhibitors (ATC group A02BC) had a growth of 9% measured in doses sold in 2009; approximately the same increase as the years before. Since 1st February 2007 lansoprazole, omeprazole and pantoprazole should be the drugs of choice in the treatment of gastro-esophageal reflux disease.[xiii]

Risk factors for developing gastric acid-related diseases are: Infection with *Helicobacter pylori,* stress, diet, use of anti-inflammatory drugs, alcohol and tobacco use, as well as age over 45. The peak for gastric ulcer development is between ages 55 and 65. Nevertheless, the people younger than 45 make up a quarter of patients receiving acid-suppressing medications in Norway (see the chart below).

Chart 2. Users of the selected proton-pump inhibitors in Norway by age. Data from 2009



Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009

3.3 Anti-depressants

Antidepressants are psychiatric medications used to alleviate mood disorders, such as major depression and dysthymia and anxiety disorders such as social anxiety disorder (Medicine net [xii]). Antidepressants are the most prescribed therapy for depression. The exact mechanism of action of antidepressants is unknown. The prevailing theory is that antidepressants increase the concentration of one or more brain chemicals (neurotransmitters) that nerve cells in the brain use to communicate with one another. The neurotransmitters affected by antidepressants are norepinephrine, serotonin, and dopamine. The different classes of antidepressants differ in the neurotransmitters they affect. This determines some of their side effects and potential drug interactions. All available antidepressants are effective, and for most cases of depression there is no good evidence that any antidepressant is more effective than another. Side effects and potential drug interactions are major factors that influence selection of antidepressants and compliance with therapy. The major antidepressant classes include: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake

inhibitors (SNRIs). These medications are among the most commonly prescribed by psychiatrists and other physicians in Norway (Medicine net [xii]). Data from the NorPD show that 292 000 individuals had at least one antidepressant prescription dispensed in 2009, women accounted for 65%. During the last three-year period the number of patients using antidepressants has remained unchanged[xiii].

The present study includes three selected preparations among the selective serotonin reuptake inhibitors (SSRIs) group. See the table below.

Table 8. Selected antidepressants - number of users per substance and year.

ATC level	Active agent	Class	Name of the original product	Number of individuals			
				2006	2007	2008	2009
N06AB04	citalopram	SSRI	Cipramil	41271	38151	35569	32859
N06AB05	paroxetine	SSRI	Seroxat	21310	19829	18698	17503
N06AB10	escitalopram	SSRI	Cipralex	76436	87539	93702	98454
TOTAL				139017	145519	147969	148816

Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009

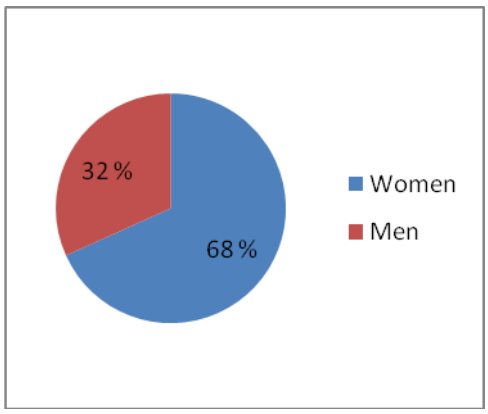
The general indications for SSRIs use is quite broad and include: major depression, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, but also social anxiety, premenstrual dysphoric disorder (PMDD), and panic attacks.

Escitalopram is noted for its high selectivity of serotonin reuptake and it is the most commonly prescribed antidepressant in Norway. Its efficacy and acceptability in the acute-phase treatment of adults with major depression is well established. Escitalopram is the *S*-stereoisomer (enantiomer) of the earlier Lundbeck drug citalopram, hence the name *es*citalopram. Despite the similarity of escitalopram and citalopram, various clinical studies have shown differentiated effects of citalopram and escitalopram, especially in severely depressed patients (Medicine net [xii]). The sales of escitalopram (Cipralex) increased by 9 % in 2009 and accounted for 33% of all antidepressants measured in DDDs. In 2009, escitalopram

had a share of 47% of the ATC group N06A measured in NOK. Escitalopram is included in the list of top 10 ranked prescription drugs according to sales.[xiii] The index group pricing system, and later the stepped price model has led to an extensive price reduction on antidepressants not covered by patent protection and where cheaper generic alternatives are available. Until 01/03/2010 escitalopram was only available in Norway in its original version – Cipralex.

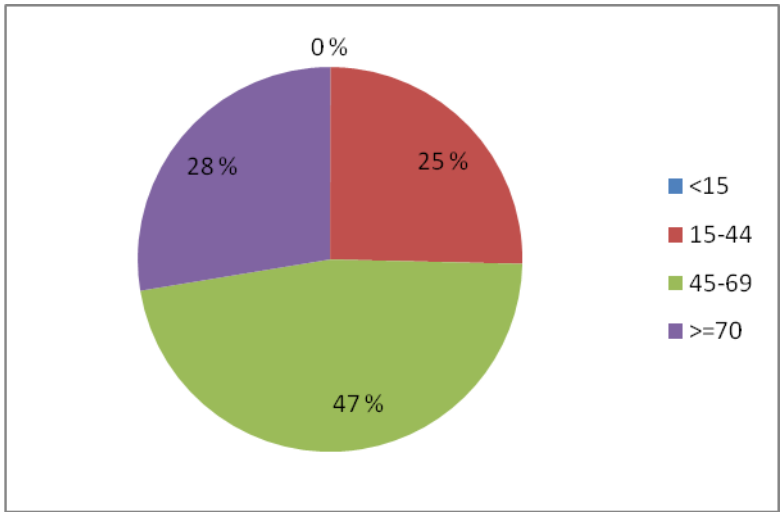
Although the precise cause of mood disorders is not known, certain factors seem to increase the risk of developing or triggering depression, including, among others: family history, traumatic experiences in childhood, stressful life events, substance dependence, presence of serious illness, certain personality traits. Mood disorders can become apparent at any age, with depression beginning typically in the late 20s. Twice as many women are diagnosed with depression as men, but this may be due in part because women are more likely to seek treatment for depression (Medicine net [xii]). See the charts below for gender and age distribution for antidepressant users in Norway.

Chart 3. Users of the selected antidepressants in Norway by gender. Data from 2009



Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009

Chart 4. Users of the selected antidepressants in Norway by age. Data from 2009



Source: Based on numeric data from Legemiddelstatistikk 2010:2 The NoPD 2005-2009

4. PRESCRIPTION DECISIONS – THEORETICAL FRAME

4.1 Patient – doctor – health care system relationships

The primary ground of each doctor's professional ethos is to protect his or her patients' life and health. This role is to be carried out in the best possible manner within a given system of resources and organization. In modern times, regardless of the form for financing of health care systems, doctors face problems of scarcity of recourses and growing costs. Progress in health technology, prolonged life expectancy combined with ageing populations in most of the developed countries, put health care systems under increasing pressure.

The vast majority of doctors (96%) surveyed by Arnesen and Fredriksen in a Norwegian study (1995) admit that the gap between what would be ideally required for their patients, and what can be offered within the national health care system, is widening and that prioritizing decisions are necessary.

The ethical guidelines of the Norwegian Medical Association emphasize the doctors' double responsibility towards patients, as well as the society in general. A doctor should safeguard interests and integrity of each individual patient [viii]. Cooperation in decision-making based on informed consent is crucial. Patients have the right to information on their health condition and therapies. At the same time, doctors are also obliged to take responsibility for common resource distribution [viii]. Lundin (2000) calls it a double-agency role and indicates the potential for moral hazard.

The moral hazard is the consequence of asymmetry in information between doctors as government's agents representing interests of both the national health care system and the patients, and their principal – the NIS (the party that commissions and pays for the agent's actions). The physicians have more information about their patient cases and about their own motivations, intentions and actions than the NIS as an institution does, as it is impossible to

monitor all doctors' action at all times. The doctors may have incentives or tendencies to behave differently (for example set their patient's interest above the budget constrains) than it would be expected of them. This is more likely to happen when the societal interest and individual interests are contradictory.

The dual nature of doctors' obligations was the subject of Arnesen's and Fredriksen's study (1995). As the result 95% of the questioned GPs experienced a conflict between their responsibility towards patients and equitable allocation of health care resources. Interestingly, most doctors also admitted that individual patients should be given priority, since the society is rather perceived as an anonymous, undefined mass.

At the same time, as indicated in the study by Sakshaug et al. (2007), the physicians feel responsible for their cost-containment role when making prescription decisions.

It seems that in order to reconcile their double-agency role, the doctors have to try to find optimal balance between the two commissions. The modern medicine ethical framework could be such as proposed by Hope et al. (1998), listing effectiveness, equity and patient choice as its key areas.

Although individual physicians can assign different weights to those three values while making their treatment decisions, the organization of health care system, with its regulations, tools and incentives, plays a fundamental role in these processes.

An introduction of the patient-list system in the Norwegian general practice in June 2001 can serve as a good example. The reform brought mayor changes to the rules of physicians' payment and introduced free choice of GPs. Before the reform, 40% of GPs' income came from the so-called "practice allowance" from the municipality and the remaining part came from the activity-based component (consultation fee and patients' out-of-pocket payment). After June 2001 the practice allowance was replaced with the capitation fee, which presently makes 30% of the GPs' income, the remaining 70% is an activity-based income. Introduction of the capitation component means that the number of patients on the individual doctor's list strongly influences their income. Patients have the right to choose their GP and change their mind up to twice a year. The GPs receive monthly reports on the number of their patients as well as which patients have joined or left their list [ix]. The reform implies a closer link between patients and their doctors, increased continuity of care and changed reimbursement system. At

the same time, general practitioners have to remain gatekeepers for the rest of the health care system. Gate-keeping role includes referrals to specialist care, issuing sickness certificates and prescribing reimbursable drugs.

Carlsen and Norheim (2003) have investigated the shift in power between physician and patient towards the patient after introduction of the patient-list system. The authors discovered that doctor's perception of their gate-keeping role has weakened. Instead, the GPs want to keep their patients satisfied and provide excellent individual service. The physicians feel that their new environment is characterized by increasing competition, higher expectations or even demands from patients and more responsibility on their part. It has become more important to meet these expectations. GPs have become more concerned about their list's length, thus its influence on their income and reputation and less concerned with reducing unnecessary resource use.

What about the interest of the society then? Do the arguments of social interest that doctors have to follow, interfere with doctor-patient relationship? Willems (2001) reminds that the discussed gate-keeping role is controversial due to the organic conflict between patient and societal interest. The duty should first of all apply to patients and not to entire populations. However, Willems argues that it is possible to integrate societal arguments into practice in morally acceptable way (2001). It is about balancing the fair distribution of health care with appropriate (effective) care for individuals within budget constraints. It is about balancing values and rationalities (Willems, 2001).

The doctor – patient relationship can be described by different models and is often of a dynamic nature. Emanuel and Emanuel (1992) are describing four different models of that relationship: paternalistic, informative, interpretive and deliberative. The comparison of these four forms is presented in the Table 5.

According to Emanuel and Emanuel (1992) a doctor-patient relationship evolved from the paternalistic one, with doctor as a guardian of the patients health and life, towards models based on mutual communication, where a doctors maintains the role of a counselor, technical expert but also becomes a friend and teacher. The authors are trying to defend models based on patient's empowerment but allowing the doctor an active role in informing, counseling and persuading the patient.

Table 9 Four Models of the Physician-Patient Relationship. Source: Emanuel EJ and Emanuel LL. "Four Models of the Physician-Patient Relationship." *JAMA* 1992, 267(16):2221-6

Patient values	**Model**	**Physician's duty**	**Concept of patient autonomy**	**Concept of physician's role**
Objective, shared by physician and patient	**Paternalistic**	Promote patient's well-being regardless of patient's current preferences	Assenting to objective values	Guardian
Fixed and known to patient	**Informative**	Provide factual information	Choice of, control over medical care	Competent technical expert
Vague, conflicting, requires elucidation	**Interpretive**	Provide factual information and help to elicit and interpret patient's values	Self-understanding relevant to medical care	Counselor or adviser
Open to development and revision through dialogue	**Deliberative**	Provide information, elicit and interpret values, articulate and persuade re: most admirable values	Moral self-development relevant to medical care	Friend or teacher

4.2 Factors affecting prescription decisions

In the era of growing use of pharmaceuticals and their costs, rational prescribing becomes increasingly important. The prescribing decisions should be most of all dictated by medical considerations, appropriateness of use and expected therapeutic effect. However, in the presence of wide range of alternative products available on the market, there are numerous other factors that contribute to the final choice of the medicine.

4.2.1 Prices

In the world of perfect competition, the price of a product is the only variable that makes a consumer choose one product over another, given that the two products are perfect substitutes.

In reality, it is difficult to find an example of such a market. The pharmaceutical markets seem to be particularly far from the ideal. These markets are characterized by very low price elasticity, thus the consumers' reactions cannot be expected to follow patterns of other markets. What about consumers' willingness to substitute or their indifference rate between two alternative medicines: original and generic? Bioequivalent preparations, though described as substitutes are often far from being perceived as such by both prescribers and their patients. To what extend then is the price a deciding factor in the choice between original and generic medications?

The physicians seem to be aware of the impact of their decisions on health care budgets. In a Canadian study by Polinski et al. (2008) as many as 87% of GPs, acknowledge an economic appropriateness of generic substitution. When it comes to clinical appropriateness, only 70% expressed their positive attitude. However, as much as 43% of GPs had limited knowledge of real drug costs (Polinski et al. 2008). So are the doctors' prescribing habits sensitive to prices? If so, are the prices paid by the patients or those paid by the insurer (or NHS) which count?

Furu et al. argue in their study on generic substitution (2008) that doctors lack direct economic incentives to let prices affect their prescription choices. The physicians can be however sensitive to their patient's preferences based on prices. This extensive Norwegian study found evidence that patients are more likely to be dispensed generics if the price difference between brand name and generic increases (results of the study summarized also in the paper by Dalen et al. 2011).

This observation was also made earlier in a Swedish study conducted by Lundin (2000), analyzing prescribing patterns for brand name vs. generic drugs. The study examines impact of several factors: price as well as patients' and doctors' acquired tastes. Lundin (2000) argues also that the answer to the question: who is paying? is fundamental when choosing between alternative versions of a medication. Patients having to pay large sums for original drug are more likely to have generic prescribed. Lundin (2000) indicates that about 60% of the change in market shares between alternative versions can be explained by differences in prices not qualifying for reimbursement. If the price difference covered by the patient increases; the doctor is more likely to prescribe a cheaper generic version (Lundin, 2000).

Similarly, the Norwegian study found that patients reimbursed by the NIS are more likely to use the brand name preparations (Dalen et al. 2011).

These results suggest that when considering prices as contributing factors to prescribing decisions, it is important to remember that it is not the price levels per se, which are important. It is most of all, costs covered by patients, determined largely by the health insurance system functioning in the study settings. Type of reimbursement schemes can make patients (and not least the doctors) either very aware or ignorant about the real drug prices. The consequences of such ignorance can have a negative effect for the public health budget. As reminded by Lundin (2000) in insurance based systems over-consumption of medical care is more likely. In a situation where most of drug costs are covered by the common insurance and where there is a possibility of prescriber's reservation against generic substitution, without impact on patients' personal costs, patients may develop an attitude of indifference towards nominal prices (and sensitivity to their own costs) of alternative preparations, keeping their preferences towards particular brands. This hypothesis, together with doctors' sensitivity towards their patients' expectations, are to some extend tested by the present study.

4.2.2 Patient's expectations

As mentioned above, along with the progress in medicine as well as the increasing access to information, the relationship between doctors and their patients evolves towards increased partnership and more patient-centered care. The character of this relationship remains in close connection with the cultural, economical and systemic settings. Again, the type of health care system organization plays a crucial role.

The 2001 primary care reform in Norway, which introduced patients' list empowered patients, giving them a free choice of their primary care physician. According to Carlsen's and Norheim's study (2003), many physicians feel that they are now under higher pressure to meet their patients' expectations in order to attract and keep them on their list.

In another study (Gulbrandsen et al., 2002), more than a half of physicians admit that sometimes or often they gave more weight to patients' wishes than to their own medical judgment. As many as six out of seven doctors sometimes or often met unrealistic demands from patients, including adjusting sickness certificate in order to help them (>50%) [Gulbrandsen et al. 2002].

Also, according to Britten (1994), most patients have clear expectations of their doctors' prescribing habits and they simply expect prescriptions. Patients might favor doctors, whose prescribing habits they accept. Dissatisfaction with prescription patterns might be a reason for which patients leave the lists (Britten 1994).

We find yet another confirmation of the patients' influence, in the Cockburn's and Pit's study (1997), where the patients who expected medications on their doctor consultation were 3 times more likely to be prescribed medication than the patients who did not have pre-visit prescribing expectations. However, doctors' perception of the patients' expectation has an even stronger impact on their own prescribing behavior. If the doctor was convinced that his patient expected prescription, this patient was ten times more likely to leave the practice with prescription than if he did in the situation when the doctor had not such assumptions (Cockburn and Pit, 1997). This suggests that doctors tend to overact to patients' expectations as perceived by their doctor when it comes to prescribing.

The doctors' tendency to overestimate patients' expectations is also mentioned in a British study by Hamilton et al. (2006).

It seems that some doctors are extensively sensitive towards their patients' expectations. Does it bring exclusively positive outcomes? Certainly not, since it can clearly lead to waste of resources. Paradoxically the doctor's reputation may also suffer. Surprisingly, Britten's study (1994) reveals that the interviewed patients were praising their doctors for not over-prescribing, not being too submissive and not giving the patients whatever they demanded.

4.2.3 Prescribing habits and brand loyalty

The period of patent protection gives the pioneering company a favorable position of an exclusive seller. The monopolist rank allows the inventor to dictate higher prices and thus recover (to various extents) the development and research costs of the new formulation. Presently the patent period after complement of all required trials is usually no longer than ten years. This, however, often proves to be sufficient to develop a strong identity (brand name, information on indications, effectiveness) of the pharmaceutical product among prescribers and patients. Both parties tend to develop habits and perceptions of quality, allowing the

original manufacturer to maintain prices on a higher level for some time, even after the cheaper competitors enter the market.

The habits can linger for both the patients and the doctors. Initial lack of, or delayed information, and ignorance about price differences can be helping the prescribers in persisting in the old habits.

For some patients it may be difficult to acknowledge that preparations with different external features can bring the same therapeutic effect (Furu et al. 2008; Dalen et al.2011).

In addition, if both patients and doctors are insulated from the additional costs of a brand-name drug compared with generic, there is no real motivation why any of the two would prefer the generic preparation over the original one (Lundin, 2000).

Prescribing habits and brand loyalty strongly correlate with prescribers' and patients' characteristics. Coscelli (2000) differentiates patient-level and doctor-level factors accountable for differentiation of bioequivalent preparations. Among the patient - related factors are: gender, age, number of prescriptions, number of doctors, number of prescribed substances and past switches between alternative medications. At the prescriber – level, quantity prescribed and brand concentration index played primary roles.

Hellerstein (1998), after studying micro-data from surveys on doctors concerning drug choice, discovered that the prescribers' variables are dominant in determining whether a patient receives prescription for original or generic drug. In Hellerstein's study, the patients' characteristics turned out to explain very little of the variation in prescriber's decision (1998).

By contrast, Furu et al. (2008), after analyzing an extensive data file from The Norwegian Prescription Database (NoPD) (study summarized in paper by Dalen et al.2011), found evidence for an influence of both physician's and patient's characteristic on the medication choice. The impact of age of both parties is particularly pronounced. The older they are, the more likely they are to have preferences for the brand-name version. Apart from the nominal age of the patients or doctors, the question of how long the patient has been using a particular preparation is also deciding. Those, who are using the generic drugs, are almost entirely new patients, who use the drug type for the first time. In addition to the age factor, male doctors were more likely to prescribe brand name product than female physicians were. The authors

also estimated that general practitioners were more likely to have patients choosing brand-name drugs when compared with patients of hospital doctors.

4.2.4 Marketing

Advertisement and other marketing tools used by manufacturers/sellers play usually a vivid role in consumers' choices. Is this also the case when it comes to medications? Advertisement of pharmaceuticals is highly regulated in Norway. Relevant legal framework has been detailed by Forskrift om legemidler, §13 (Regulations for Pharmaceuticals)[x]. According to the law [x], advertising directed to the public is only allowed for approved OTC (over-the-counter) preparations and only in specified media. When it comes to POD (prescription-only-drugs) such advertisement can only be directed to health professionals (doctors, dentists and veterinary doctors) through direct channels (without the media). They can only contain basic information about the medicines and cannot be accompanied by any objects, gifts, services, premiums or anything that presents economical value. In addition, the named health personnel are banned from accepting such benefits. Free samples can be sent to the specified health professionals only at their own requisition and only in quantity of one sample of a specific medicine per year. [x] Despite these strict regulations, the pharmaceutical industry makes use of other channels to stream down their marketing activities. According to the NoMA's report (Madsen, 2003), doctors are the industry's most important cooperates, and GPs make their key target group. The report estimates that the industry's marketing expenditure in Norway reaches over 500 million NOK annually. The doctors' need for continued education, guidelines on new treatments and new medicines, which is often fulfilled by training sessions, individual meetings with drug consultants, seminars, conferences (often involving foreign trips), are sponsored or heavily subsidized by the pharmaceutical industry. Incomes from adverts are also important source of financing for medical magazines. Many patients' organizations rely on subsidies from pharmaceutical companies.

All these activities certainly have their effect on prescribing and use of drugs. The NoMA as a state agency and regulatory body, appreciates the industry's legitimate need for marketing of their products. Nevertheless, NoMA postulates more transparency around this cooperation,

better reporting on marketing activities, and making such information publicly available (Madsen, 2003).

4.2.5 Other factors

Furu et al. (2008) found that in the Norwegian settings pharmacies play an active and important role in the ultimate choice between substitutable alternatives. In absence of the prescriber's reservation against generic substitution, the actual decision on the drug version takes place in the dispensing pharmacy.

Pharmacies are obliged to offer a preparation at the lowest price level – the stepped- price (NoMA, 2008), as well as to provide information of the pharmaceutical. Patients can either accept the version recommended by the pharmacy or insist on having the brand – name product. In this case, the patients cover the additional price difference.

Furu et al. (2008) discovered that pharmacy identity is important in convincing patients to accept generic substitution. The authors suggest that time and effort that pharmacy personnel spend on persuasion are strongly influenced by economical incentives, strictly pharmacy margins, which are affected by procurement prices and varied among different pharmacy chains. This would explain why some pharmacy chains report higher levels of patient reservation against generic substitutions than others do.

Another explanation might be that the original may be available at the stepped price in one or some of the pharmacy chains. This would lead to a lower patient reservation rate.

Another factor listed by Furu et al. (2008) is the so called "market age" of generic competitors. In younger competition markets the brand - name loyalty plays in important role (Furu, 2008), and it weakens as the information and experience with the new alternatives spreads.

4.3 Discussion around generic substitution

The generic substitution system can serve as a very efficient tool in forcing more competition in the pharmaceutical sector and helping with containing escalating costs in the other parts of the national health care. It can prove to be also satisfactory to other parties: pharmacy wholesalers, chains and generic producers, at least in economical terms. The possibility of using cheaper alternatives is valuable to most patients, who cover entirely or partially the cost of their drug therapies.

Due to increasing drug expenditures, several Western European countries with both tax and insurance-based financing of the health care have introduced some sort of generic competition, either in form of generic prescribing or generic substitution at dispensing.

There is however some controversy around the use of generics instead of the brand-name products. The recent debate on generics in the UK can serve as an example. Last year's attempt of introduction of the automatic generic substitution (similar to the one functioning in Norway) by the Department of Health evoked so much protest from doctor and patient groups that the proposal had to be abandoned. Apart for the usual arguments of varying bioavailability and problems with adherence (which I describe more in detail below), the adversaries raised the issue of responsibility for health outcomes, in situation when the medication would be substituted at the pharmacy counter and the prescriber would not be aware of the substitution. Prescribing in the UK looks however a little different than in Norway. Traditionally, prescribers in the UK have been using the active substance name on the prescription. Generic prescribing has already reached a high 83% (Solanki, 2009) and the General Practitioners Committee estimated that an automatic generic substitution would result in about 0,4% of drug cost reduction. Such a comparatively small saving to the National Health Service (NHS) was probably the reason why the proposal was ultimately rejected.

The major sources of controversies around generic substitutions are presented below.

4.3.1 Problems with compliance

Chemist and pharmacists understand that generics are in fact substitutable to the brand name, although the products often appear to be different. Patients however, are more interested in the medication's name, form, taste, appearance, in other word everything that can be perceived by them and can make it easy or difficult for them to carry out pharmacological therapy.

Danger of misunderstanding and improper use of pharmaceuticals can have serious consequences. As pointed out by Aarseth (2001), significant number of patients in general wards are hospitalized because of side effects or incorrect use of pharmaceuticals. For these reasons, patient's adherence is crucial.

According to the NICE clinical guideline [xi], adherence is defined as "the extent to which the patient's action matches the agreed recommendations", thus it primarily requires a consensus between the patient and the prescriber about the use of medication. According to the Guide [xi], non-adherence is therefore seen as a basic limitation in delivery of health care, and not merely the patient's problem. This initial consensus requires the patient's involvement in the decision to prescribe and access to information and support from the health provider's side, i.e. both from the prescriber and the pharmacist dispensing the medicine.

Opponents of generic substitution often argue that a patient can receive the same substance, but with different name, appearance and dosing schedule on each visit to the pharmacy (Solanki, 2009), which can leave them confused. The problem is particularly pronounced for elderly patients or/and those who suffer from chronic conditions. Older people take often several drugs, and it is harder for them to stick to their regiments thus they are more likely to have an adverse drug reaction. In a study quoted by Solanki (2009), over 30% of elderly (60 years and over) patients prescribed antidepressants, were on drug regiments of at least eight different pharmaceuticals. Some of the patients were taking as many as 20 different drugs daily. For obvious reasons such patients develop their administration routines, based on appearance of the medicines as well as on their packaging. In case of older patients, the correct use of medicines can be also sabotaged by poor eyesight and confusion. This can easily lead to a situation, where the patients take incorrect dose or forget to take the medicine altogether.

The recent Norwegian study (Håkonsen and Toverud, 2011) discovered that as many as 10% of the studied patient population (Pakistani immigrants in Oslo on long-term medicines), were mistakenly using more than one equivalent generic preparations at the same time. The incorrect use of medicines was more likely for patients who used more than one pharmacy and those who had problems with receiving complete information about the dispensed pharmaceuticals.

The simplest way to improve compliance among patients is to ensure good communication, which should flow in both directions. Most patients want to be involved in the decision-making process, and the more involved they are the better understanding of their own therapy they have; the more likely they are to comply with it. Good doctor-patient relationship and clear written instructions also improve patients' adherence (MERC, 1997).

To counteract the dangers or non-compliance, NoMA requires the products within the same substitution groups, apart from the same strength, to have the same pharmaceutical form (oral tablets/capsules can be only substituted by oral tablets/capsules) and approximately the same size of the packaging (though small variations are acceptable). The scheme also gives prescribers the right to reservation against automatic substitution. This is possible when doctors predict a high probability for the individual patients' non-compliance.

4.3.2 Bioavailability

Another argument of the antagonists of generic substitution is varying bioavailability.

According to the European Medicines Agency (EMEA/CPMP: 2001), bioavailability of generics has to lie between 80% and 125% of the original branded medicine. This means potentially that patients, who are being often switched between different generic medicines, could receive a medicine with 125% bioavailability on one occasion, and 80% on the next. This would mean a 36% loss in bioavailability. If the patient were switched back to the 125% bioavailability medicine, they would experience a 45% increase in bioavailability. Such a change can affect the clinical outcomes for the patient. Meredith's study (2003) emphasizes that the issue of average bioavailability can be particularly problematic in case of drugs with

very narrow or very broad therapeutic range especially when confronted with high subject variability (both between different subjects and within the same subject).

However bioequivalence studies quoted by Madsen et al. (2008) show that, the variation in bioequivalence is most often less than 3%. Such differences have no clinical effect and are smaller than variation naturally found within the same subjects, which can be as high as 60% from one day to another.

The MERC manual (MERC, 1997) also confirms that the actual differences in bioequivalence between generic and trade-name drugs approved by FDA (The US Food and Drug Administration), are on average 3.5% and rarely exceed 10% in any single study.

4.3.3 Changed effect and adverse effects

Another problem often raised in the debate on generic substitution is the issue of changed effect and adverse effects (Madsen et al. 2008). It is claimed that non-active substances in generic preparations can cause allergic reactions and that the medicine itself causes different effects than the original drugs.

Despite scarce documentation and evidence of the side effects, a Norwegian study exploring patients' attitudes towards generics 3 years after introduction of the generic substitution (Kjønniksen et al. 2006), found that every third patient who had their medicine substituted reported negative experiences.

The NoMA registers and evaluates each report of side effects. As argued by Madsen et al. (2008), after examining 400 reports of incidents of adverse effects, NoMA found no evidence of serious adverse effects, which would be due to the preparation itself. This suggests that problems arise mainly due to the incorrect use of medication rather than the drug's composition.

The system also gives prescribers the right to reserve against generic substitution, in case individual patients report allergic reactions to some of the preparation's ingredients.

4.3.4 Believes and attitudes

Finally, there come arguments from outside of the scientific world. According to the German study by Himmel (2005), over one-third of the patients who declared they knew the difference between the branded-name and generic products, were skeptical towards generic because of their lower price. Some of the questioned patients were convinced that generic prescribing was "invented" to solve financial problems of the insurer on the patients' expense (Himmel, 2005). The German patient population is not isolated in the way they perceive generic medications. The results of the Norwegian study (Kjønniksen et al. 2006) quoted earlier, also suggest that psychological factors and prejudices can play significant role. Many people are convinced that lower price equals lower quality. One quarter of the patients interviewed for the Håkonsen's and Toverud's study (2011), expressed an opinion that generic alternatives were counterfeit drugs and their effects were poorer.

An earlier study by Håkonsen et al. (2009) indicated that patients' negative attitude towards generics were strongly associated with number of drugs used, education level and insufficient information concerning substitution.

Researchers agree that an individual approach, providing thorough and comprehensive information on medications by prescribers to their patients is fundamental. It can help to counteract negative effects of transition from brand name to generic use, and even change the patients' attitudes.

4.4 Hypotheses

The present study aims at examining and determining potential predictors of variation in doctors' reservation level across different substances. Although the author appreciates the underlying reasons based on true medical considerations as well as those based on believes, the performed analyses focuses on economical (non-medical) and geographical determinants of prevalence in doctors' reservation notes. In particular the influence of pharmaceutical prices raised both by Lundin (2000) and Furu et al. (2008), (though in wider context of prescribing decisions), is going to be tested in this thesis in the specific context of doctors' reservation notes.

The recent study on NorPD data (Furu et al. 2008 and Dalen et al., 2011) including 23 different substances (both reimbursable and non-reimbursable prescription drugs); found that patients are more likely to end up with generic products when the price difference between the original and generic alternatives increases. However the authors discovered also that patients who have their medication reimbursed (those with the so-called "blue prescription") are more likely to choose the brand name preparation.

These results suggest that generally the price difference does matter, but its effect can be somewhat slowed down by the type of prescription (reimbursable vs. non-reimbursable).

The present thesis uses data on reimbursable drugs only and is going to test if the price difference can impact the proportion of reservation notes made by doctors. In other words, the author seeks to find out if doctors are sensitive to their patients' preferences/requests motivated economically. In particular, I hypothesize that the larger the price difference is, the more likely it is that the physician makes a reservation to save the patient from extra expenses.

In addition, some of other variables will be tested as potential predictors. Pharmacy chains (similarly to the study by Furu et al 2008), level of centrality (geographical location of dispensing pharmacy), type of pharmaceutical and their association with the level of doctors' reservations will be analyzed.

5. METHODS AND DATA

5.1 Study design

Cross-sectional numerical data derived from two extensive datasets (The National Prescription Database in Norway and pharmacy reservation reports) was gathered, merged, aggregated and prepared for statistical analysis using descriptive statistics and binary logistic regression. Time periods selected included: June 2006, June 2007, June 2008, June 2009 and June 2010; and covered the set of 9 selected substances, making up 23 substitution groups. The obtained dataset includes monthly records from all community pharmacies (hospital pharmacies were not included) in Norway, covering a number of variables (listed in a section below) and aggregated at the level of municipalities and pharmacy chains.

A mini focus group with 6 general practitioners from Eastern Oslo area was also performed to obtain professional opinions about the hypotheses, as well as to capture observations and attitudes towards generic substitution and doctors' role in the scheme. Another mini focus group with representatives of the three biggest pharmacy wholesalers was organized in the final stage of the study to obtain their comments on the results. The results were also presented at the NoMA Department of Pharmaco-economics and the Department of Medical Information, some of the related remarks have been included in the discussion section (Chapter 7).

5.2 Databases

The National Prescription Database in Norway (Nor PD) was established on 1 January 2004 to gather data on the use of prescription-only drugs (POD). The Norwegian Institute of Public Health (FHI) has been since in charge of running the register. The main idea behind starting the database was to improve knowledge about the use of pharmaceuticals as well as describing characteristics of both prescribers and users, thus raising the rational use of medicines in general [xiv].

NorPD contains data on prescription drugs dispensed from all Norwegian primary pharmacies on monthly basis. It does not include the sales of over-the-counter drugs (OTC). Pharmacies register the data electronically and the information is made anonymous on the individual doctor's and patient's level. Identity numbers of patients or their doctors are replaced with sequence numbers (pseudonyms). This allows maintaining the link between prescription and these individuals without abusing their privacy. Even though one person could have a medication prescribed more than once, the medication will be calculated according to their real number, while the user will be counted only once.

The data is registered on an individual level and include characteristics of the user, medication, prescriber and these of the dispensing pharmacy. The following table presents the information registered in NorPD.

Table 10. Data registered in NorPD

Data level	Data registered in NorPD
User	Pseudonym (sequence number), year and month of birth, gender, municipality
Medication	Item number, number of packages, refund section, price, price proportion paid by user, date for dispensing
Prescriber	Pseudonym (sequence number), year of birth, gender, profession, specialization
Pharmacy	License number, municipality

Source: Based on the information on NorPD by FHI [xiv]

A number of reports derived from NorPD are readily available to the population, such as: number of users of particular substances (also by gender and age group, region or county), prevalence use per 1000 inhabitants, sales values in NOK, sales volume in DDDs (Defined Daily Doses, term defined below).

Data on reservations (both those made by doctors and by patients) come from monthly reports from pharmacies to FHI. The data is aggregated on the level of individual pharmacies per item number per month.

5.3 Data

For the present analyses, NorPD and reservation records for nine substances across three indication groups, included in the stepped price system, were chosen. The table below presents the substances selected. Each of them is coded according to the ATC (Anatomical Therapeutic Chemical) classification system. These nine substances are subject to further classification into 23 substitution groups. The initial raw data contained information aggregated on the municipality and pharmacy chain level reported in June for years 2006-2010 (5 time points) for every product containing any of the 9 active substances dispensed. The dataset included 66 489 observations (rows) across 36 variables (columns). There were 10 637 observations for 2006, 12 312 for 2007, 13 351 for 2008, 13 897 for 2009 and 16 292 observations for 2010. Numerical data crucial for performing the statistical analyses was either originally expressed or re-calculated by the author into the common unit – Defined Daily Doses (DDDs). Below the concepts of ATC classification system, substitution groups and Defined Daily Doses are defined more in detail.

Table 11. Selected substances by indication and inclusion in substitution list

ATC code	Active agent	Class	Main indication	Included in the stepped-price system/substitution scheme *
A02BC01	omeprazole	PPI	Gastric ulcer	Before 2004
A02BC02	pantoprazole	PPI	Gastric ulcer	01/12/2007
A02BC03	lansoprazole	PPI	Gastric ulcer	01/05/2005
A02BA02	ranitidine	H2-receptor antagonists	Gastric ulcer	Before 2004
C10AA01	simvastatin	HMG CoA reductase	High cholesterol	Before 2004
C10AA03	pravastatin	HMG CoA reductase	High cholesterol	15/10/2004
N06AB04	citalopram	SSRI	Depression	Before 2004
N06AB05	paroxetine	SSRI	Depression	01/05/2004
N06AB10	escitalopram	SSRI	Depression	01/03/2010

PPI= Proton pump inhibitor, SSRI= Selective Serotonin Reuptake Inhibitor

*generic substitution was established on 1 April 2001; stepped-price system was established on 1 January 2005

5.3.1 Anatomical Therapeutic Chemical (ATC) Classification System

The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of pharmaceuticals. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC), and was first published in 1976. In the ATC system the drug substances are classified into groups at 5 different levels. The classification system divides drugs into different groups according to target organ of the system, mechanism of action, and chemical and therapeutic properties. Each bottom-level ATC code stands for a pharmaceutically used substance in a single indication (or use). The drugs are divided into fourteen main groups (1st level), with one pharmacological/ therapeutic sub-group (2^{nd} level). The 3rd and 4th levels are chemical/pharmacological/ therapeutic sub-groups and the 5th level is the chemical substance. (Legemiddelstatistikk 2010:2 • Folkehelseinstituttet).

Table 12. ATC groups

ATC main groups	Main therapeutic/indication area
ATC group A	Alimentary tract and metabolism
ATC group B	Blood and bloodforming organs
ATC group C	Cardiovascular system
ATC group D	Dermatologicals
ATC group G	Genito - urinary system and sex hormones
ATC group H	Systemic hormonal preparations, excl. sex hormones and insulins
ATC group L	Anti-neoplastic and immunomodulating agents
ATC group M	Musculo-skeletal system
ATC group N	Nervous system
ATC group P	Anti-parasitic products, insecticides and repellents
ATC group R	Respiratory system
ATC group S	Sensory organs
ATC group V	Various

5.3.2 Substitution groups

The NoMA publishes a substitution list which includes interchangeable medicines. Each product is assigned to the relevant substitution group. Pharmaceuticals must be approved as equivalent and interchangeable to be classified within the same substitution group. In practice it means that apart from containing the same active substance they have to be of the same strength and the same form of administration, i.e. pills can be only interchangeable with pills and dissolvable tablets with dissolvable tablets. Each active substance (each ATC code) can be represented by one or more substitution groups, only of different strengths or forms. Within one substitution group there can be brand-name products, generic versions of the original medicine or products coming from parallel import, all with the individual product number. Each of the substitution groups is assigned the stepped price by NoMA, and the pharmacies are obliged to have at least one preparation within each substitution group available at the stepped price. The catalogue of substitution groups chosen for these analyses can be viewed in the appendix.

5.3.3 Defined Daily Doses (DDDs)

Defined daily doses (DDDs) are a statistical measure of drug consumption established by WHO and used internationally. DDDs are used to standardize the comparative usage of various drugs between themselves or between different health care environments.

Norwegian Prescription Database defines a DDD as "the assumed average maintenance dose per day for a drug used for its main indication in adults. It is important to be aware that in many cases the prescribed dose may deviate from the DDD. The DDD should only be considered as a technical unit of measurement." [xiv]. Using DDDs allows for comparison between alternative medications, regardless of price differences. In addition, the evaluation of drug consumption volumes over time, nationally and internationally, is simplified and improved by the use of DDDs. The DDDs are determined on the basis of evaluation of international use of the substance in question, bearing in mind that national therapy traditions (indications, dosages) often differ greatly. Drugs used for more than one indication may cause particular problems which are important to consider when evaluating statistics based on

DDDs. With the exception of a very few specially formulated pediatric preparations, adult dosages are used [xiv].

5.4 Variables

As mentioned above, the dataset includes 66 489 observations (rows) across 36 variables (columns), specifying (among others): date, municipality, county, level of centralization, pharmacy chain, product code, packing description, ATC code, administration form, strength, number of DDDs per packing, prescription group, substitution group number, original vs. generic, turnover in number of packages, doctor's reservation in packages, patient's reservation in packages, turnover in DDDs, doctor's reservation in DDDs, patient's reservation in DDDs, sales in PRP, value covered by the patient in PRP, price PRP, part of PRP covered by patient, maximum PRP, stepped price.

5.4.1 Dependent variable

The doctors' reservation level in DDDs, labeled as "DocRes" is in the centre of all the analyses performed. It has been calculated as a proportion of doctors' reservation in DDDs to turnover in DDDs. The results obtained were numbers within the interval [0;1] for the great majority of the rows, except for 212 outliers (22 values below 0 and 190 values greater than 1). Since the outliers represented only 0.31 % of all 66 489 observations, the author decided to keep the outliers in the dataset, as they were values as reported from the pharmacies and they might have reflected some corrections in reporting on sales/reservations. For the analyses using descriptive statistics it was necessary to weigh the obtained observations by the corresponding turnover in DDDs. In this way the aggregation was represented in every observation and the real means could be calculated.

5.4.2 Independent variables

"Delta" – continuous variable, representing the price difference between branded and generic preparations within the same substitution group, expressed in NOK/DDD.

The construction of this independent variable is crucial for the analysis of the influence of economic incentives in the model and was extensively discussed (among the author and the supervisors). The price difference has been calculated by deducting the stepped price from the maximum retail price (PRP). In this case only that price difference is relevant because the usual patient's co-payment (before 2011 = 36%) would be the same for all the three following scenarios, but the effective expense would only be different if they opposed the substitution without doctor's reservation:

1. The patient accepts generic substitution – the patient pays the usual co-payment (36% of the stepped price, which can be entered into their co-payment card for reimbursable drugs)

2. The patient gets the original medication with the doctor's reservation on it – the patient still pays only the usual co-payment

3. The patient rejects substitution and agrees to cover the difference him/herself (patient's reservation) – the patient has to pay the usual co-payment and cover the price difference between the price of the original preparation and the stepped price

Therefore the only factor influencing the doctors' (and their patients') decision on the final choice (also about making a reservation or persuading the doctor to make one) would be the additional price difference, that would have to be covered out of the patient's pocket. Although the real prices may vary across pharmacy chains, the figures for the reimbursed portion of cost remain the same across the pharmacies, and as such are available for doctors to view via the catalogue.

Pharmacy chain – categorical variable covering five categories, coded in the following way: AP1 - Apotek 1 coded as 1, VAP –Vitus Apotek, coded as 2, BAP – Boots Apotek coded as 3, DAP - Ditt Apotek coded as 4, UDA – independent pharmacies, coded as 5. For AP1, VAP, DAP, and UDA dummy variables were created. BAP served as the reference (baseline) category.

ATC codes – representing the three selected pharmaceutical groups - categorical variable covering three categories, coded in the following way: A* - acid modifying drugs – 1; C* -

statins- 2, N* - antidepressants – 3. Dummy variables were created for anti-acid and anti-depressive drug categories, leaving statins to serve as the reference group.

Level of centralization – categorical variable standardized and used by the Statistics Norway (Statistisk Sentralbyrå), describing the geographic location of a municipality in relation to urban settlements of various sizes. The urban settlements are divided into three levels according to population and available public services. Urban settlements at level 3 are regional centers (population at least 50 000), level 2 settlements have a population between 15 000 and 50 000, and level 1 settlements have a population between 5 000 and 15 000. To describe the available alternatives for work travels to one or several urban settlements, the municipalities are divided into four centrality levels [xv]:

- Sentrale kommuner (urban municipalities) – Central municipalities that include an urban settlement at level 3 (regional centre) or are within 75 minutes (90 minutes for Oslo) travel from the centre of an urban settlement (central municipalities) – in the present analyses coded as 1
- Noe sentrale kommuner (smaller urban municipalities) – Fairly central municipalities that include an urban settlement at level 2 or are within 60 minutes travel from the centre of an urban settlement – in the present analyses coded as 2
- Mindre sentrale kommuner (less central municipalities) – includes fairly remote municipalities that include an urban settlement at level 1 or are within 45 minutes travel from the centre of an urban settlement – in the present analyses coded as 3
- Minst sentrale kommuner (least central municipalities) - includes remote municipalities that do not meet the requirements for travel time from urban settlement – in the present analyses coded as 4

If a municipality fulfills the requirements to centrality on more than one level, the highest of these levels applies.
Dummy variables were created for urban municipalities, less central and the least central municipalities. The smaller urban category was used as the baseline.

5.5 Statistical tools and analyses

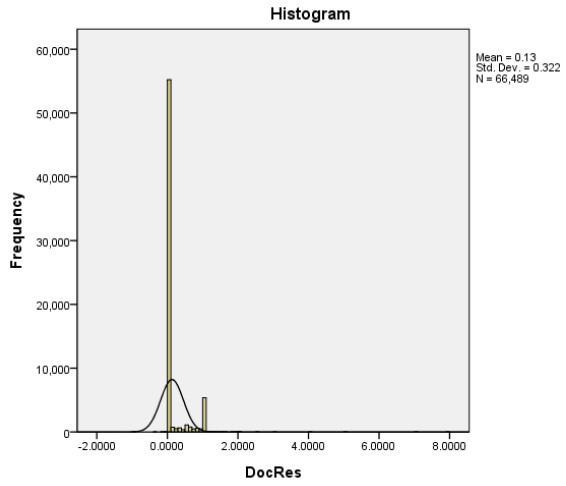
PASW Statistics (formerly SPSS) version 18 was used to perform the quantitative analyses of the dataset.

5.5.1 Descriptive statistics

The analysis of the distribution of the dependent variable (DocRes) was performed using histogram and descriptive statistics. Weights of the corresponding turnover values in DDDs were applied to reflect the aggregation hidden in each individual row (observation). As the result 71 842 471 DDDs were obtained from 66 489 rows of aggregated original reports.

The analyses of frequencies and histograms were also performed separately for each of the periods. The obtained distributions for doctors' reservation level (both weighted and non-weighted) proved to be far from normal, with large variations, substantial difference between mean and median, with the median value equal to zero. The attempts towards "normalizing" of the distribution were not successful. The table below presents basic descriptive for the variable.

Table 13. Basic descriptive statistics and histogram for DocRes



Doctors' reservation level		
N	Valid	71842471
	Missing	0
Mean		.050457
Median		.000000
Std. Deviation		.1896315
Variance		.036
Range*		8.9930
Minimum*		-1.0000
Maximum*		7.9930

* Values from outside the [0, 1] interval are result of the occurrence of outliers discussed above

In addition descriptive statistics for DocRes have been run across all of the independent variables to provide an overview of variation and base for analyses using logistic regression. The next chapter contains relevant tables and description of the findings.

5.5.2 Binary Logistic Regression

The author has decided that using the binary logistic regression will be the most appropriate (compared with, for example, a linear regression) for of analyses for the following reasons:

- The distribution of the dependent variable – doctors' reservation level (DocRes) is far from being normal (alternative use of linear regression would produce unreliable results),
- The dependent variable (DocRes) is a proportion, which takes values in the range 0.0 to 1.0 representing probability values. It would be illogical to try to extrapolate values beyond this interval.

It is important to note, that due to the choice of binary logistic regression, the independent variable changes its character from being continuous within the interval [0; 1] into becoming binary with values either 0 or 1. Therefore each line representing so far the aggregated monthly data from each pharmacy chain for each municipality becomes equally weighted individual report case coded for either presence or absence of doctors' reservation notes.

This type of variable is called a Bernoulli (or binary) variable, as only two types of outcomes are possible: the doctor makes a reservation note or he/she does not. Proportions and probabilities are different from continuous variables in a number of ways. They are bounded by 0 and 1, whereas in theory continuous variables can take any value between plus or minus infinity. This means that normality for a proportion cannot be assumed, and therefore a binomial distribution has to be assigned. Unlike the normal distribution, the mean and variance of the Binomial distribution are not independent. The mean is denoted by P and the variance is denoted by $P*(1-P)/n$, where n is the number of observations, and P is the probability of the event occurring (e.g. the probability of doctors' making a reservation note). Since logistic regression calculates the probability or success over the probability of failure, the results of the analysis (or measures of an effect size), are in the form of an odds ratio.

Odds = p/(1-p),

The logarithm of p/(1-p) is called the logit, and maps probabilities onto the scale of the linear predictor in logistic regression. The log odds is the logarithm of the odds of the probabilities (Pallant, 2007).

Like ordinary regression, logistic regression can be extended to incorporate more than one explanatory variable, which may be either quantitative or qualitative. The logistic regression model can then be written as follows (Bewick et al. 2005):

$\text{logit}(p) = a + b_1x_1 + b_2x_2 + \ldots + b_ix_i$

where p is the probability of doctors making a reservation note on prescription and x1, x2 … xi are the explanatory variables (predictors).

Applying logistic regression with the assumptions of a large sample size and absence of multicollinearity among the predictors (independent variables) can provide answers to questions such as which variables are important in determining whether a doctor makes a reservation note or not.

The large sample size requirement is fulfilled thanks to the extensiveness of the dataset. Since there is no formal way in the logistic regression to test for multicollinearity in SPSS (Pallant, 2007) and the predictors (independent variables) are very few and representing very distinct categories, the author is assuming absence of multicollinearity among them.

For performance of the binary logistic regression procedure, it was necessary to introduce a modified dependent variable (BinaryDocRes) with two possible values: 0 for the lines when doctors' reservation did not occur at all (DocRes = 0), and 1 for all positive values of DocRes (DocRes > 0).

Five binary logistic regressions were performed separately for each of the five periods, introducing BinaryDocRes as the dependent variable and the following variables as predictors: delta, centralization (along with 3 dummies), pharmaceutical group (2 dummies) and pharmacy chain (4 dummies). The reference group was made up of records for the reservation level for statins sold by the Boots pharmacy in a smaller urban municipality. The separate analyses for individual categories of pharmaceuticals as well as a regression with pooled records for all the periods was also performed, to capture any changes in effects.

6. RESULTS

6.1 Descriptive statistics

Mean doctors' reservation levels have been calculated across all of the independent variables and presented below. It has been noted that there might have been a problem with the data for 2008, as the doctors' reservation level is consistently lower across all independent variables than in remaining periods. The author has attempted to find the reason (with the help of NoMA), however no explanation was found. Since the results for 2008 are not contradictory to the trends for the four other periods, the 2008 data was included in the analyses.

Delta

The table contains "Delta" values - the price differences between branded and generic preparations within the same substitution group, expressed in NOK/DDD for all five periods (June 2006-2010) across all 23 substitution groups as well as corresponding mean doctors' reservation level (DocRes) reported within these groups for the same point of measurement.

One can observe a big variation in DocRes, both among different pharmaceutical groups, as well as within the groups themselves. For example, among the acid suppressing drugs some preparations (Ranitidin) have DocRes below 1% while others (Omeprazol) oscillate on the level of 25-42%. Such differences can also be observed among statins: Simvastatin (DocRes at 5%) vs. Pravastatin (15.5%) and antidepressants: Escitalopram (2-4%) vs. Paroksetin – 13%. However, it is difficult to match it with the variability in "delta". For some of the highest values of DocRes, "delta" can be either relatively high or, on the contrary, lie in the lower range of "delta" values. There seems to be no obvious correlation between the "delta" values and the corresponding DocRes proportions. These results will be tested further with the help of the logistic regression.

Table 14. Mean price differences (delta) vs. mean doctors' reservation levels, years 2006-2010

ATCcode	SubG	Substitution group name	Δ 2006	Δ 2007	Δ 2008	Δ 2009	Δ 2010	D.Res'06	D.Res'07	D.Res'08	D.Res'09	D.Res'10
A02BA02	000012	RANITIDIN BRUSETABLETTER 150MG*	0,00	0,00	0,00	0,00	0,00	0,0325	0,0271	0,0000	0,0000	0,0000
A02BA02	000013	RANITIDIN TABLETTER 150MG	0,00	0,00	0,00	0,51	0,51	0,0210	0,0163	0,0010	0,0027	0,0013
A02BA02	000014	RANITIDIN TABLETTER 300MG	0,00	0,00	0,00	0,00	0,00	0,0311	0,0210	0,0003	0,0011	0,0001
A02BA02	000015	RANITIDIN BRUSETABLETTER 300MG	0,00	0,00	0,00	0,03	0,03	0,0252	0,0180	0,0000	0,0000	0,0000
A02BC01	000023	OMEPRAZOL TABLETTER 10MG**	6,57	4,45	7,88	7,78	3,36	0,3790	0,5144	0,4189	0,4681	0,4234
A02BC01	000024	OMEPRAZOL TABLETTER 20MG	6,25	5,22	4,81	3,41	1,16	0,2110	0,2600	0,2616	0,2648	0,2547
A02BC02	001420	PANTOPRAZOL ENTEROTAB 40 MG****			5,83	5,79	5,89			0,0154	0,0044	0,0017
A02BC02	001525	PANTOPRAZOL ENTEROTAB 20 MG****			5,84	5,76	4,76			0,0037	0,0032	0,0014
A02BC03	000028	LANSOPRAZOL ENTEROKAPSLER 30MG***	7,95	8,60	7,83	7,46	10,27	0,0123	0,0143	0,0018	0,0031	0,0015
A02BC03	000938	LANSOPRAZOL ENTEROKAPSLER 15MG***	9,40	10,47	8,54	7,90	8,04	0,0084	0,0105	0,0003	0,0018	0,0023
C10AA01	000251	SIMVASTATIN TABLETTER 10MG	0,00	0,00	0,00	3,99	4,62	0,0411	0,0354	0,0007	0,0435	0,0545
C10AA01	000252	SIMVASTATIN TABLETTER 20MG	0,00	0,00	0,00	4,20	1,56	0,0362	0,0342	0,0007	0,0407	0,0434
C10AA01	000253	SIMVASTATIN TABLETTER 40MG	0,00	0,00	0,00	2,45	2,10	0,0351	0,0417	0,0006	0,0363	0,0401
C10AA01	000254	SIMVASTATIN TABLETTER 80MG	0,00	0,00	0,00	3,00	2,72	0,0389	0,0698	0,0006	0,0551	0,0607
C10AA03	000261	PRAVASTATIN TABLETTER 20MG	6,22	7,42	7,64	10,16	7,54	0,1122	0,1717	0,1482	0,1465	0,1404
C10AA03	000853	PRAVASTATIN TABLETTER 40MG	5,79	5,45	6,29	5,44	4,74	0,1447	0,1535	0,1601	0,1642	0,1704
N06AB04	000656	CITALOPRAM TABLETTER 10MG	6,69	7,44	7,56	7,66	6,23	0,0631	0,0806	0,0346	0,0685	0,0514
N06AB04	000657	CITALOPRAM TABLETTER 20MG	4,15	4,61	4,68	3,66	3,53	0,1019	0,1043	0,0959	0,1085	0,1043
N06AB04	000658	CITALOPRAM TABLETTER 40MG	3,90	4,27	4,20	3,97	3,47	0,0200	0,0000	0,0000	0,0000	0,0000
N06AB05	000661	PAROKSETIN TABLETTER 20MG	2,43	2,53	2,16	2,15	0,96	0,0942	0,0906	0,0832	0,1436	0,1377
N06AB10	000671	ESCITALOPRAM TABLETTER 10MG*****	1,38	1,30	2,31	2,48	2,36	0,0000	0,0000	0,0000	0,0000	0,0313
N06AB10	001651	ESCITALOPRAM TABLETTER 5MG*****					2,86					0,0271
N06AB10	001652	ESCITALOPRAM TABLETTER 20MG*****					1,98					0,0391

*Only original has been available on the market

**Usually prescribed to children

*** Original not available on the market

****Original (Somac) available at stepped price at all pharmacy chains

***** Original (Cipralex) available at stepped price at one of the pharmacy chains in 2010

Pharmacy chain

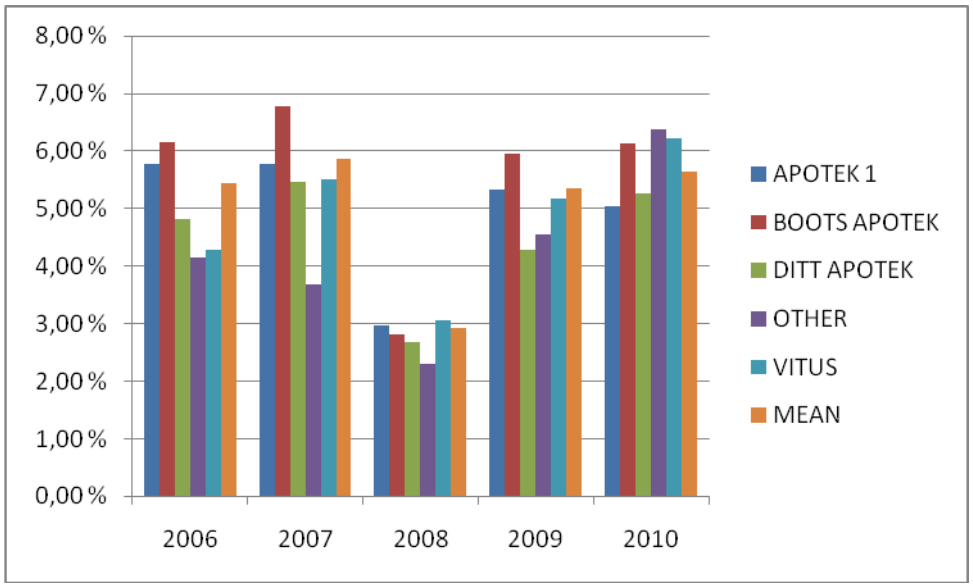
There is a noticeable variation in DocRes across different pharmacy chains, with substantial differences between the maximum and minimum values. See the table below.

Table 15. Level of doctors' reservations by pharmacy chain, years 2006-2010

	2006	*Std.dev.*	2007	*Std.dev.*	2008	*Std.dev.*	2009	*Std.dev.*	2010	*Std.dev.*
APOTEK 1	**0,0578**	*0,1915*	**0,0577**	*0,1918*	**0,0297**	*0,1578*	**0,0534**	*0,1926*	**0,0504**	*0,1974*
BOOTS APOTEK	**0,0616**	*0,1561*	**0,0679**	*0,1831*	**0,0282**	*0,1666*	**0,0595**	*0,2050*	**0,0613**	*0,2125*
DITT APOTEK	**0,0483**	*0,2024*	**0,0547**	*0,1794*	**0,0268**	*0,1570*	**0,0429**	*0,2153*	**0,0527**	*0,2134*
OTHER	**0,0416**	*0,1715*	**0,0367**	*0,1846*	**0,0230**	*0,1547*	**0,0455**	*0,1870*	**0,0638**	*0,2068*
VITUS	**0,0429**	*0,1690*	**0,0551**	*0,1584*	**0,0306**	*0,1373*	**0,0517**	*0,1929*	**0,0622**	*0,2153*
MEAN	**0,0543**	*0,1852*	**0,0587**	*0,1857*	**0,0293**	*0,1594*	**0,0536**	*0,2008*	**0,0564**	*0,2060*

However these differences show also some dynamics in terms of internal results for individual chains throughout different years, as well as ranks that the pharmacy chains take in comparison with their competitors (see the Chart below). For example, independent pharmacies (category: other) had in the first four years the DecRes in the lowest range, and for 2010 they report the highest level of reservations.

Chart 5. Level of doctors' reservations by pharmacy chain, years 2006-2010



Level of centralization

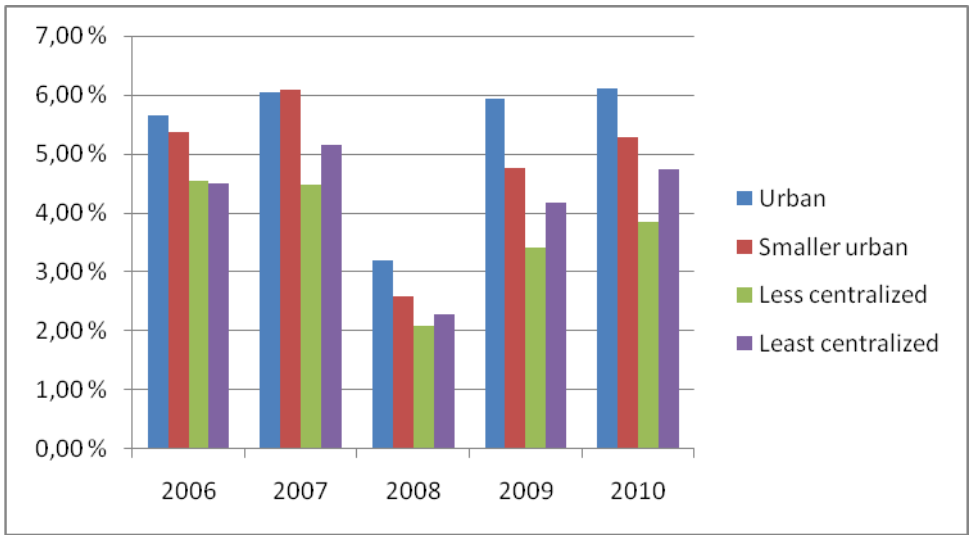
There is a considerable variation in the level of doctors' reservation, and more importantly, this variation is very consistent across the analyzed periods. See the table below.

Table 16. Level of doctors' reservations by centrality level, years 2006-2010

	2006	*Std.dev.*	2007	*Std.dev.*	2008	*Std.dev.*	2009	*Std.dev.*	2010	*Std.dev.*
Urban	**0,0566**	*0,1852*	**0,0606**	*0,1862*	**0,0320**	*0,1665*	**0,0593**	*0,2099*	**0,0612**	*0,1945*
Smaller urban	**0,0536**	*0,1846*	**0,0608**	*0,1889*	**0,0258**	*0,1478*	**0,0476**	*0,1886*	**0,0528**	*0,1842*
Less centralized	**0,0454**	*0,1789*	**0,0447**	*0,1683*	**0,0210**	*0,1332*	**0,0341**	*0,1585*	**0,0385**	*0,1630*
Least centralized	**0,0450**	*0,1906*	**0,0516**	*0,1885*	**0,0229**	*0,1499*	**0,0418**	*0,1882*	**0,0475**	*0,1850*

Urban and smaller urban municipalities clearly score highest on the reservation level, while less centralized tend to report the lowest proportions of doctors' reservations.

Chart 6. Level of doctors' reservations by centrality level, years 2006-2010



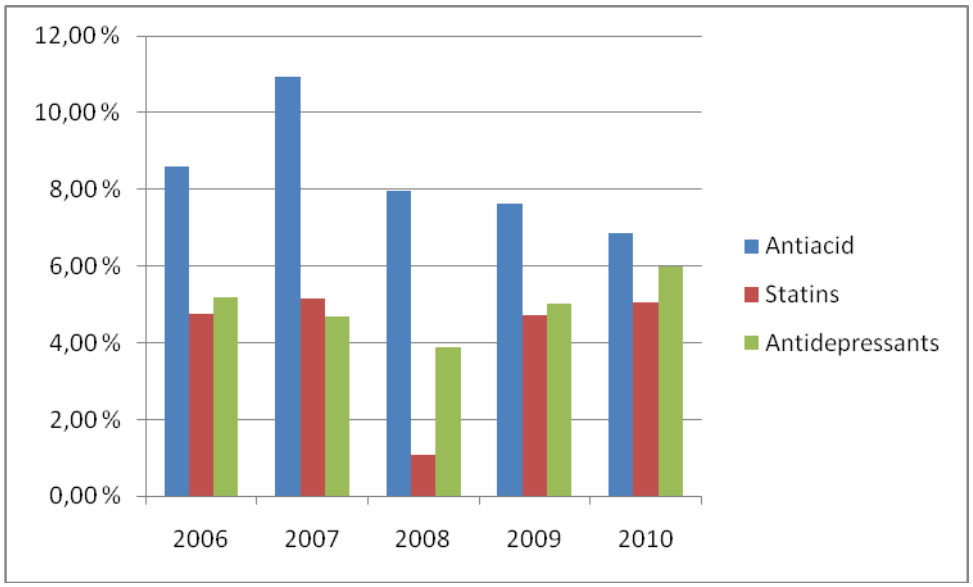
Pharmaceutical group

Acid-modifying drugs show consistently the highest level of doctors' reservations when compared with the two other selected pharmaceutical groups. Moreover, this difference presents as substantial, though appears to be a bit smaller in the last year of the analysis.

Table 17. Level of doctors' reservations by ATC gruop, years 2006-2010

ATC code	**2006**	Std.dev.	**2007**	Std.dev.	**2008**	Std.dev.	**2009**	Std.dev.	**2010**	Std.dev.
antiacid	**0,0859**	*0,2550*	**0,1095**	*0,2868*	**0,0795**	*0,2542*	**0,0764**	*0,2527*	**0,0686**	*0,2370*
statins	**0,0476**	*0,1520*	**0,0514**	*0,1476*	**0,0107**	*0,0984*	**0,0472**	*0,1797*	**0,0507**	*0,1972*
antidepressant	**0,0519**	*0,2023*	**0,0468**	*0,1877*	**0,0387**	*0,1815*	**0,0502**	*0,2013*	**0,0598**	*0,1965*
TOTAL	**0,0543**	*0,1852*	**0,0587**	*0,1857*	**0,0293**	*0,1594*	**0,0536**	*0,2008*	**0,0564**	*0,2060*

Chart 7. Level of doctors' reservations by ATC gruop, years 2006-2010



6.2 Logistic regression

Binary logistic regression was performed separately for each of the five time points, as well as for pooled data for all periods, to assess the impact of the independent variables on the likelihood that doctors make a reservation note on a prescription. As mentioned previously, a modified version of the dependent variable (BinaryDocRes) had to be introduced. The new BinaryDocRes can take only one of the two possible values: 0 for the lines when doctors' reservation did not occur at all (DocRes = 0), and 1 for all positive values of DocRes (DocRes > 0).

All the independent variables were inserted in the model as predictors.

Table 18. Results of binary logistic regression by year.

	2006			2007			2008			2009			2010		
Predictor	**B**	**Sig.**	**Exp(B)**	**B**	**Sig.**	**Exp(B)**	**B**	**Sig.**	**Exp(B)**	**B**	**Sig.**	**Exp(B)**	**B**	**Sig.**	**Exp(B)**
Delta	.070***	.000	1.073	.036***	.000	1.037	.000***	.000	1.000	-.001***	.000	.999	-.001***	.000	.999
urban(1)	.191**	.002	1.210	.218***	.000	1.244	.193**	.005	1.212	.300***	.000	1.350	.139**	.007	1.149
less_centralized(1)	-.191*	.065	.826	-.071	.433	.931	-.208*	.067	.812	-.054	.564	.947	-.251**	.004	.778
least_centralized(1)	-.199**	.021	.820	-.229**	.005	.795	-.271**	.007	.762	-.133	.104	.876	-.196**	.006	.822
AP1(1)	-.260***	.000	.771	-.155**	.008	.856	.344***	.000	1.411	-.415***	.000	.660	-.140**	.014	.869
VAP(1)	-.043	.563	.958	-.019	.771	.981	.050	.530	1.052	-.072	.300	.931	-.157**	.008	.855
DAP(1)	-.100	.324	.905	.044	.641	1.045	-.176	.195	.838	-.145	.210	.865	-.176*	.077	.839
OTHER(1)	-.265*	.072	.767	-.348**	.006	.706	-.163	.285	.850	-.304**	.009	.738	-.106*	.278	.899
antiacid(1)	1.263***	.000	3.535	1.257***	.000	3.516	-.303***	.000	.739	1.707***	.000	5.513	1.711***	.000	5.535
antidepressants(1)	.757***	.000	2.132	-.716***	.000	2.047	-.492***	.000	.612	.703***	.000	2.020	.612***	.000	1.845
Constant	-2.180***	.000	.113	-1.966***	.000	.140	-2.192***	.000	.112	-1.995***	.000	.136	-1.947***	.000	.143

*p < 0.1; **p < 0.05; ***p < 0.001. Baseline: Statins dispensed at Boots pharmacy in smaller urban centres

B-value: equivalent to regression coefficient; Exp(B) – odd ratio (OR)

The model contained one continuous independent variable: delta - the price difference between branded and generic preparations within the same substitution (variable entered without modifications), and three categorical variables: centrality level, pharmacy chain, pharmaceutical group (variables entered as dummies). The reference group was made up of records for reservation level for statins sold by the Boots pharmacy in a smaller urban municipality. Due to the utilization of dummy variables the coefficient values on individual categorical variables need to be interpreted as relative to their reference (baseline) groups. The reference group for all five periods tested is the same.

The main results have been gathered in the table below. The complete PASW output can be viewed in the appendix.

All five logistic regression analyses run on the full set of independent variables (predictors) for the years 2006-2010 scored significant (.000, which really means $p < 0.0005$) on the Omnibus test of model coefficients. This test challenges goodness of fit test and shows how well the model performs without predictors entered into the model (Omnibus tables with Chi-square values for each regression available in the appendix with PASW output). Since the test proved to be significant for all five regressions, one can conclude that the model built was able to distinguish between cases where doctors' reservation did occur and where it did not occur. The model had a varied explanatory power for different years (see model summaries in the appendix with PASW output), and for example, in 2010 explained between 9.6% (Cox and Snell R square) and 15.3% (Nagelkerke R square) of the variance in reservations' proportion.

B values – values in the equation. Negative values mean that an increase in the independent variable score will result in the decreased probability of the case reporting a score of 1 (doctors' making a reservation note).

The Exp (B) columns show values for odd ratios (OR) for each of the independent variables. Odd ratio is a relative measure of probability that an event occurs to that it does not occur. Odd ratios represent the change in odds of being in one of the categories of outcomes relative to the other, when the value of a predictor increases by one unit (Pallant, 2007). For example, in 2010 the odds that the doctor puts a reserving note on prescription, relative to not writing a

reserving note is a little higher (1.149 times higher) for urban areas than for the reference group (here the smaller urban areas), all factors being equal.

Below, the main findings across all independent variables are discussed.

Delta

As indicated in the analysis of descriptive statistics, it is difficult to draw any ultimate conclusions about dependence of DocRes on the delta. For the first year of the analysis (2006), a 1 NOK/DDD of increase in difference in prices between original and generic medicines, resulted in the odds ratio that the reservation will occur being equal to 1.073 (a slight increase in likelihood that doctors decide to guard against substitution). The following period this effect was even weaker (Exp (B) = 1.037), then there was no effect at all, and for the last two periods there is an extremely small negative effect. Although regression coefficients proved significant ($p < 0.001$) for all five periods, the effect size is predominantly very small, for all of them and the direction of the effect is very inconsistent (positive for the first two periods and negative for the two last periods). The results for pooled analyses for all five periods was consistent with the findings for individual time periods, ie. (Exp (B) = 0.999, $p < 0.001$).

The author chooses to remain skeptical towards calling the association meaningful, and concludes that the price difference between original preparation and its generic counterpart does not have a direct influence on the doctors' reservations level.

Pharmacy chain

As observed in the descriptive part, there is a variation in DocRes among different pharmacy chains. In the logistic regression analysis, some of these differences proved significant, some did not. The level of Doc Res for Apotek1 (AP1) was significantly lower (odds ratio from 0.66 in 2009 to 0.869 in 2010), apart from 2008 (OR: 1.411) than that of Boots (in the baseline), all other factors being equal. The DocRes for Vitus pharmacy (VAP) was not significantly different from the reference, except for 2010 (OR: 0.855). Ditt Apotek (DAP) did not score significant as a factor at all. The DocRes reported by the independent pharmacies (OTHER), have always proved lower that the baseline, with varied significance

though. Pharmacy chain identity as a variable is a potentially influential factor of the level of DocRes.

Level of centralization

The big variation in DocRes and its consistency presented in the descriptive part of the analysis, for the centralization variable, have found their confirmation in the logistic regression part. Regression coefficients for urban areas have scored positive and significant for all five periods (ORs: from 1.149 in 2010 to 1.35 in 2009) in reference to the baseline. Less and least centralized areas noted lower level of DocRes than the baseline category (smaller urban), with varied significance, however. That means that urban municipalities consistently report more doctors' reservations than the remaining municipalities and there is a clear correlation between the two variables here.

Pharmaceutical group

The influence of type of pharmaceutical have proved to be significant and very stable in the regression analysis. The acid – modifying drugs (antiacid) represent higher level of DocRes in four out of five analyzed periods (OR: from 3.516 in 2007 to 5.535 in 2010) in relation to the reference groups (statins), all other factors being equal. Significant effects, but with a changing direction is noted for antidepressants. One can conclude that identity of a pharmaceutical, and its area of action plays an important role in prescribing preferences.

6.3 Limitations and strengths of the analyses

Due to the use of a logistic regression, the dependent variable as well as many of the categorical variables had to be changed into binary coding. For the DocRes this meant that regardless of the individual value of the proportion (whether it was 0.001 or 1), they were given a value 1 (DocRes present), as long as it was bigger than 0 (DocRes not present).

As the effect of the underlying binominal distribution, the parameters of such a model cannot be estimated in exactly the same way as for simple linear regression. Instead, the parameters are usually estimated using the method of maximum likelihood (Bewick et al. 2005).

Although all the models built for individual years scored as significant, the average achieved R square values (Cox and Snell's as well as Nagelkerke's) were at the level of 0.1 and did not exceed 0.17 (see the tables in appendix), suggesting that the model is not very useful in predicting whether the doctors will make a reservation note on prescription or not. Although the contribution of many of the explanatory variables in the prediction of DocRes is statistically significant, the effect size is restricted.

It has been also noted that there might have been problems with the dataset for 2008, which remained unexplained. Although the results for that year were not contradictory with findings for remaining periods, knowledge of possible reasons for data aberrations would have added some value to the analyses.

Despite of these disadvantages, the present study presents a simple method to track and measure potential explanatory power for a number of independent variables. The use of descriptive statistics provides a clear introduction into the discussed problems. In the situation where normality of distribution of the variables cannot be assumed, the use of logistic regression provided means for modeling the dependence of a binary response on explanatory variables, not restricted to linear effects. In addition, the large sample sizes can ensure that obtained results are robust.

7. CONCLUSIONS AND DISCUSSION

The results from the present study suggest that the main hypothesis about direct impact of the price difference between branded and generic versions of pharmaceuticals on the doctors' reservations level remains unsupported. The association between the two variables proved neither strong nor consistent. That suggests that economical motives of patients do not incline their doctors to guard against substitution. At the patient's level, it is not the price difference, which prompts them to convincing their doctors to make a reservation. The earlier study by Dalen and colleagues (Dalen et al. 2011) concluded that the difference in prices does matter when it comes to generic vs. brand name prescribing, ie. the bigger the difference the more likely that generic version is prescribed. However this effect applied to prescription drugs in general. In the same study, the type of prescription (reimbursable vs. non-reimbursable) proved to have a strong impact: patient with reimbursable drugs were more likely to end up with brand name versions.

Compiling the findings of this thesis with the study by Dalen et al. (2011), one can draw a common conclusion that for the patients who are indifferent to the brand of their medication, the price is an important factor of their final choice and they are more likely to accept generic substitution. However, to those patients, as well as their doctors, who have developed strong preferences towards brand name products, there are other important factors, which influence the decision on opposing substitution with generics, rather than the price difference.

The performed analysis found strong and consistent association between centralization and doctors' reservation levels. Urban and smaller urban municipalities show increased doctors' reservation levels when compared with smaller/more remote centers. These findings confirm increased patients' power triggered by stronger competition among GPs in bigger centers. They are also in line with the opinions of the focus group doctors':

"Patients in cities are more aware of their choice possibilities"- says one doctor. Another one adds:

"Before I started practicing in Oslo, I was a doctor in the province. And there is a big difference in what patients require from doctors, in terms of referrals for example, smoking

cessation and so on. So when you live in Oslo, you are clearer about what you want from your doctor. I want this, I want that. They know which medicine they want to have and they tell their doctor. I want this and this. So we (doctors) *have to be bit more service oriented here* (in Oslo)."

Others add:

"It is expected, that it's us (doctors) *who take the decision* (about the reservation note) *according to our rules. But it doesn't work like this with these patients. They in fact are the ones that decide."*

"It is often the patients who ask for it (the reservation note). *They* (the patients) *have been to the pharmacy, where they got the information on the substitution, they become anxious about the effectiveness and side-effects, get the information from the pharmacist that their doctor can just write a note on the prescription, and this way they get the original drug. Later, they come to their doctor, with such an order in mind and it is difficult to turn it down. At least I don't use that much time on it. They say "in the pharmacy they told me that you can just write the note".*

Another possible explanation (as suggested by Dr. Bjørg Nitteberg Sørensen, NoMA), is that doctors in more central areas are influenced by contact with the pharmaceutical industry to a much higher degree, than in more dispersed parts of the country. They take part in more meetings and seminars arranged by pharmaceutical companies, and are more often visited by the companies' representatives. Specialists in big university hospitals (located in big cities) also receive a special attention from the pharmaceutical industry, and their acquired attitude towards original or generic medicines can easily spread from the hospital environment to the primary health care level along with the first prescription.

Yet another interesting aspect of the centralization level importance is that the role of pharmacies is different in less urbanized areas than big cities. The observation was raised both by the focus group doctors and the pharmacy wholesalers' representatives. The respondents from both groups agreed that the flow of information between doctors, pharmacies and patients is better in smaller centers. Pharmacies have more contact with doctors; in cases of hesitation pharmacists can contact the doctors more easily. And doctors usually know the

assortments of local pharmacies, so the cooperation between all involved parties goes more smoothly.

As described by one of the doctors: *"The pharmacists in rural areas know the patients as well as their doctors, they can offer more individualized information. The doctor knows that Mrs. Hansen gets usually the green pills and knows that Mrs.Larsen from the pharmacy knows it as well."*

The focus group doctors think that the difference is also down to the time pharmacists dedicate to individual patients: "*They have more time for the patients", "The patients in small pharmacies get better information and better service"*. However, the pharmacies` representatives did not confirm that, claiming that there was no difference in service time across pharmacies in more or less urbanized areas.

When it comes to the pharmacy chain identity as an influential factor modulating doctors` reservation level, the obtained results are in line with the earlier study by Dalen et al. (2011), which discovered that pharmacy efforts are important in convincing patients to accept generic substitution. The authors argued that the input from pharmacy personnel on promoting particular products is strongly influenced by economical incentives, strictly pharmacy margins, which are affected by procurement prices and varied among different pharmacy chains. This would explain why some pharmacy chains report higher levels of patient reservation against generic substitutions than others do.

The focus group doctors agreed that a strong decision power lies with the pharmacies; this is where the actual substitution takes place and where the patients get their information from:

"So what the pharmacist tells the patient is also very influential. They often say to patients "if you react in another way to the yellow pills than to the red ones, then you have to tell your doctor to make a note on your prescription."

The present analysis found that there tends to be a significant difference when it comes to doctors' reservation levels between various pharmacy chains. This difference, however, is dynamic in time and different pharmacy chains "score" various ranks in different periods of time. In theory this may be due to some pharmacies having original products as "preferred" product, thus making doctors reservations unnecessary. But according to the pharmacy

chains' representatives, Somac has been the "preferred" stepped price product for all the chains since the substance became part of the stepped price model (2008). One of the chains obtained a deal on Cipralex (in the stepped price model from March 2010). But apart from these, generics have been the preferred products sold at stepped price. So except for Cipralex/Escitalopram in 2010, the differences between the chains may not be explained by brand-deals held by individual pharmacy chains. Despite the variation in policies and deals, the representatives claim that the resulting differences in doctors' reservation levels have no deeper meaning. All the chains operate in one small market, uniform surroundings, the same regulation system, they respond to the same third party payer (NIS), they overall have similar policies, and they all take part in the generic substitution scheme.

Another variable, which turned out to be an important predictor of variation in doctors' reservation level, is pharmaceutical group. Acid-modifying drugs show consistently the highest level of doctors' reservations when compared with the two other selected pharmaceutical groups. One of the underlying reasons can be that effectiveness of this group of drugs is more observable to patients than that of statins.
Another factor causing variation here can be external regulation. Since June 2005, Simvastatin is the "preferred medicine" or the drug of choice for all new and old statin users.
What about the dramatic differences among different drugs from the same groups of drugs? The variation in doctors' reservation levels can be very big, for example, Omeprazole: as high as 40% vs. Ranitidine – less than 1%, or Paroxetin – 14% vs. Escitalopram -3-4% (for more examples see the table 14. in the Chapter 6.

In single cases, the fact that some original versions of medicines are available at the stepped-price (Pantoprazol - Somac, see Table 14.), results in low reservation levels, since there is no practical need for it. For these cases the real preferences may remain veiled and non-reflected in the data on reservations.

The doctors from the focus group admit that prescribing habits play a dominant role:

"One hasn't got the whole catalogue in the head. The habit is strong. The doctor does not wonder 'which one should I prescribe today?'"

"Once I have written the prescription, I don't use any more time on it. It's very rare that I remember to inform the patient that they can be dispensed a preparation with a different name, but it's ok. I must admit I rarely do that."

They also think that the history of the pharmaceutical product very often influences the prescription decisions:

"The medicines which are first in the market, which people are accustomed to for years. The ones that came later, they are more indifferent to. It can be also that there is a real difference."

"In many cases these other drugs have been tried out before".

In some doctors' opinion there are simply differences in how various preparations work:

"It often happens, like for example for Pravachol, that those medicines which are more rarely prescribed, tend to be more prompt to have reservation. If you decide for Pravachol, you want a concrete brand and there is a reason behind it."

This would indicate that some pharmaceuticals have higher rates due to their clinical specification. Pravastatine (original Pravachol), has a higher reservation rate, as explained by Dr. Steinar Madsen (NoMA), as it is more often prescribed to patients with particular problems with reactions to pharmaceuticals, for example patients after transplantations or patients receiving very many medicines (possible interactions).

Apart from the variables – predictors tested in the thesis, the interviewed doctors indicated many other reasons behind variation in doctors' reservation levels. Most often they were referring to patients' characteristics, like age, and ethnicity, which confirms the finding of other recent Norwegian studies on generic substitution (Dalen et al. 2011; Håkonsen and Toverud 2011). Here are some of the opinions:

"What is often the big problem are the immigrant patients, who don't understand or misunderstand the information. They make me personally write the note on the prescription to make sure they follow my information correctly; or the elderly who misunderstand. They get the new packet of medicine before the old one is finished, and then they are left with two

boxes at home with different names on them, so they end up taking both medicines. It does happen quite a lot."

"For elderly patients I always write the note against substitution. But we don't know always about those medicines which have generic counterparts, we don't know the names, so I feel I have no control over this".

In the opinion of the pharmacy chains' representatives, the absence or presence of a reservation note is sometimes a question of doctors' characteristics or simply of the computer system they use for prescription. They gave examples that at some practices the reservation note is set as default function.

Summarizing, the quest for factors that influence doctors to guard against generic substitution remains unexhausted, and the model presented in this thesis can be expanded. Disaggregating the used dataset to a more individual level is, unfortunately, not possible (since the pharmacy reservation data report presents aggregated figures at monthly level), however, adding new data on, for example, marketing expenditure of pharmaceutical companies, could help explore the influence of marketing directed to doctors.

A well functioning generic substitution system is in the interest of a healthy pharmaceutical market, as well as individual patients, and the society in general. One of the focus group doctors concluded:

"I don't think there is a big problem with it now. When it started it was terrible. All patients were asking about it. There was lots of confusion. Now, I think, most are used to the system."

It seems that in the Norwegian setting, after a decade in use, despite some challenges, it can be called a success.

Notes

[i] Legemiddelindustrien "Tall og Fakta 2011" (The Association of the Pharmaceutical Industry in Norway, "Facts and figures 2011")

http://www.lmi.no/media/1197884/tall-og-fakta-2011_web.pdf

[ii] Apotek of Legemidler 2010. Apotekforeningen (Norwegian Pharmacy Association), Oslo Ferbuary 2010

http://www.apotek.no/Default.aspx?ID=49&ShowIpaper=30

[iii] http://www.legemiddelverket.no/upload/26982/Om%20apotekavanse%202011_2.pdf

[iv] http://www.helfo.no/privatperson/egenandeler/Sider/default.aspx

[v] OECD Health Data 2010: Statistics and Indicators

http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH

[vi] §6-6 LOV 2000-06-02 nr 39: The Norwegian Pharmacy Act. Website Lovdata:

http://www.lovdata.no/all/hl-20000602-039.html

[vii] http://www.legemiddelverket.no/templates/InterPage____80412.aspx

[viii] The Norwegian Medical Association. Etiske regler for leger. 1961, 2002

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[ix] HELFO Regular GP scheme

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[x] LOVDATA FOR 2009-12-18 nr 1839: Forskrift om legemidler (legemiddelforskriften) Kapittel 13. Reklame for legemidler

http://www.lovdata.no/for/sf/ho/xo-20091218-1839.html#map017

[xi] NICE clinical guideline 76, Medicines adherence, January 2009

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[xii]Medicine net

http://www.medicinenet.com

[xiii] Drug Consumption in Norway 2005-2009

http://www.legemiddelforbruk.no/

[xiv] The Norwegian Prescription Database, The Norwegian Institute of Public Health

http://www.norpd.no/

http://www.stattucino.com/HelpFiles/logreg.html

[xv] http://www3.ssb.no/stabas/ItemsFrames.asp?ID=5285601&Language=nb

[xvi] http://www.legemiddelverket.no/upload/131266/20091125_apotekdekning.pdf

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Appendix 1. PASW Output

Descriptive statistics

Report

DocRes

ATC code	Mean	N	Std. Deviation
antiacid	.081026	12893659	.2549090
statins	.041353	42401205	.1615336
antidepressant	.049963	16547608	.1941429
Total	.050457	71842471	.1896315

DocRes * Årmåned

DocRes

Årmåned	Mean	N	Std. Deviation
2006	.054322	10991001	.1852413
2007	.058670	13301872	.1857367
2008	.029311	14407609	.1594259
2009	.053580	15823968	.2008030
2010	.056432	17318021	.2059994
Total	.050457	71842471	.1896315

Report

DocRes

Byttegruppekode	Mean	N	Std. Deviation
000012	.012260	241030	.0708390
000013	.007881	908240	.0499617
000014	.008980	882767	.0640786
000015	.008559	247110	.0630494
000023	.443703	94712	.4721963
000024	.253050	3728880	.4095786
000028	.006310	3613077	.0464592
000251	.034814	1167018	.1398985
000252	.030982	11487964	.1239552
000253	.030665	22329936	.1285401
000254	.045825	4347756	.1759167
000261	.142611	751088	.3326664
000656	.059427	207085	.2030776

000657	.102912	4329509	.2879979
000658	.002855	68644	.0376766
000661	.108596	2612951	.2658982
000671	.006982	8676998	.0504770
000853	.157835	2317443	.3459432
000938	.004009	259955	.0436223
001420	.005920	2282408	.0237778
001525	.002516	635480	.0218830
001651	.027079	94021	.0885483
001652	.039062	558400	.1399809
Total	.050457	71842471	.1896315

Report

DocRes

Kjedekode	Mean	N	Std. Deviation
AP1	.049588	31890722	.1875571
VAP	.049281	18648891	.1901165
BAP	.055426	15778251	.1955412
DAP	.046106	3175139	.1822430
UDA	.044085	2349468	.1824603
Total	.050457	71842471	.1896315

Report

DocRes

Sentralitet	Mean	N	Std. Deviation
urban	.054073	46312851	.1944655
smaller urban	.048073	13455968	.1841961
less centralized	.035967	5215467	.1630188
least centralized	.041728	6858186	.1849599
Total	.050457	71842471	.1896315

Report

DocRes

Sentralitet	Årmåned	Mean	N	Std. Deviation
urban	2006	.056591	7236089	.1852025
	2007	.060550	8624778	.1861770
	2008	.032014	9300829	.1665034
	2009	.059332	10227511	.2099051
	2010	.061150	10923644	.2117979

	Total	.054073	46312851	.1944655
smaller urban	2006	.053615	2121344	.1846403
	2007	.060786	2551176	.1889100
	2008	.025831	2625788	.1478110
	2009	.047555	2830487	.1886083
	2010	.052785	3327173	.2001328
	Total	.048073	13455968	.1841961
less centralized	2006	.045410	667197	.1788733
	2007	.044734	958176	.1682725
	2008	.020954	1057778	.1332337
	2009	.034117	1197552	.1584702
	2010	.038511	1334764	.1750232
	Total	.035967	5215467	.1630188
least centralized	2006	.045039	966370	.1906047
	2007	.051595	1167743	.1884648
	2008	.024278	1423214	.1499175
	2009	.041809	1568419	.1881985
	2010	.047493	1732440	.2008395
	Total	.041728	6858186	.1849599
Total	2006	.054322	10991001	.1852413
	2007	.058670	13301872	.1857367
	2008	.029311	14407609	.1594259
	2009	.053580	15823968	.2008030
	2010	.056432	17318021	.2059994
	Total	.050457	71842471	.1896315

Report

DocRes

Kjedekode	Årmåned	Mean	N	Std. Deviation
AP1	2006	.057787	4941399	.1915239
	2007	.057650	5931835	.1918190
	2008	.029732	6138966	.1577723
	2009	.053405	7108164	.1925706
	2010	.050415	7770359	.1973627
	Total	.049588	31890722	.1875571
VAP	2006	.042868	2447963	.1561272
	2007	.055113	3148459	.1831119
	2008	.030581	4030180	.1666178

	2009	.051675	4144829	.2050334
	2010	.062152	4877460	.2124945
	Total	.049281	18648891	.1901165
BAP	2006	.061607	2586225	.2024367
	2007	.067867	3105186	.1794115
	2008	.028236	3251764	.1570307
	2009	.059470	3398521	.2153338
	2010	.061261	3436554	.2133606
	Total	.055426	15778251	.1955412
DAP	2006	.048266	750396	.1715288
	2007	.054701	733059	.1846422
	2008	.026807	528710	.1546739
	2009	.042910	550344	.1870314
	2010	.052704	612630	.2067888
	Total	.046106	3175139	.1822430
UDA	2006	.041577	265017	.1689983
	2007	.036736	383334	.1583748
	2008	.023035	457989	.1372825
	2009	.045542	622111	.1928687
	2010	.063756	621017	.2153282
	Total	.044085	2349468	.1824603
Total	2006	.054322	10991001	.1852413
	2007	.058670	13301872	.1857367
	2008	.029311	14407609	.1594259
	2009	.053580	15823968	.2008030
	2010	.056432	17318021	.2059994
	Total	.050457	71842471	.1896315

Report

DocRes

ATC code	Årmåned	Mean	N	Std. Deviation
antiacid	2006	.085882	1590487	.2550245
	2007	.109488	1939262	.2868228
	2008	.079538	2650000	.2541906
	2009	.076384	3155422	.2527151
	2010	.068570	3558488	.2369864
	Total	.081026	12893659	.2549090
statins	2006	.047564	6329368	.1519731

	2007	.051391	7946062	.1476079
	2008	.010693	8696691	.0983950
	2009	.047154	9582374	.1796820
	2010	.050696	9846710	.1972459
	Total	.041353	42401205	.1615336
antidepressant	2006	.051905	3071146	.2022573
	2007	.046753	3416548	.1876522
	2008	.038726	3060918	.1814695
	2009	.050219	3086173	.2013240
	2010	.059829	3912823	.1964855
	Total	.049963	16547608	.1941429
Total	2006	.054322	10991001	.1852413
	2007	.058670	13301872	.1857367
	2008	.029311	14407609	.1594259
	2009	.053580	15823968	.2008030
	2010	.056432	17318021	.2059994
	Total	.050457	71842471	.1896315

Report

Delta

ATC code	Årmåned	Mean	N	Std. Deviation
antiacid	2006	4.955367	1590487	2.9791950
	2007	4.785560	1939262	3.1563654
	2008	266.774853	2650000	1.1378325E3
	2009	243.671882	3155422	1.0774606E3
	2010	212.376837	3558488	957.0227647
	Total	174.406903	12893659	902.3131920
statins	2006	.537813	6329368	1.5373120
	2007	.470019	7946062	1.6213917
	2008	.366328	8696691	1.4291378
	2009	2.908735	9582374	.9399797
	2010	2.278817	9846710	.9757085
	Total	1.430056	42401205	1.6941616
antidepressant	2006	2.398271	3071146	1.1302770
	2007	2.409526	3416548	1.3260146
	2008	2.566647	3060918	1.1249917
	2009	2.584070	3086173	.8625928

	2010	2.297510	3912823	.8988233
	Total	2.442567	16547608	1.0845243
Total	2006	1.696925	10991001	2.3344990
	2007	1.597333	13301872	2.4258956
	2008	49.834462	14407609	498.7360349
	2009	50.855447	15823968	490.6704602
	2010	45.453747	17318021	442.0444246
	Total	32.707641	71842471	387.9610964

PASW output - Binary logistic regression

1. Output for binary logistic regression for the **year 2006** only. Baseline: smaller urban Boots pharmacy, reservation level for statins.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	521.118	10	.000
	Block	521.118	10	.000
	Model	521.118	10	.000

Chi-square and **Sig.** - This is the chi-square statistic and its significance level. The value given in the Sig. column is the probability of obtaining the chi-square statistic given that the null hypothesis is true. In other words, this is the probability of obtaining this chi-square statistic (521.118) if there is in fact no effect of the independent variables, taken together, on the dependent variable. This is, of course, the p-value, which is compared to a critical value, perhaps .05 or .01 to determine if the overall model is statistically significant. In this case, the model is statistically significant because the p-value is less than .000.

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	10603.830[a]	.048	.074

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

Classification Table[c]

Observed			Predicted					
			Selected Cases[a]			Unselected Cases[b]		
			BinaryDocRes		Percentage	BinaryDocRes		Percentage
			.00	1.00	Correct	.00	1.00	Correct
Step 1	BinaryDocRes	.00	8325	5	99.9	43211	2379	94.8
		1.00	2305	2	.1	10240	22	.2
	Overall Percentage				78.3			77.4

a. Selected cases Årmåned EQ 1

b. Unselected cases Årmåned NE 1

c. The cut value is ,500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Delta	.070	.009	63.190	1	.000	1.073
	urban(1)	.191	.060	10.035	1	.002	1.210
	less_centralized(1)	-.191	.103	3.406	1	.065	.826
	least_centralized(1)	-.199	.086	5.305	1	.021	.820
	AP1(1)	-.260	.063	17.168	1	.000	.771
	VAP(1)	-.043	.075	.334	1	.563	.958
	DAP(1)	-.100	.102	.973	1	.324	.905
	OTHER(1)	-.265	.148	3.235	1	.072	.767
	antiacid(1)	1.263	.063	403.116	1	.000	3.535
	antidepressants(1)	.757	.061	156.185	1	.000	2.132
	Constant	-2.180	.120	327.324	1	.000	.113

a. Variable(s) entered on step 1: Delta, urban, less_centralized, least_centralized, AP1, VAP, DAP, OTHER, antiacid, antidepressants.

2. Output for binary logistic regression for the **year 2007** only. Baseline: smaller urban Boots pharmacy, reservation level for statins.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	622.742	10	.000

	Block	622.742	10	.000
	Model	622.742	10	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	12450.743[a]	.049	.075

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

Classification Table[c]

			Predicted					
			Selected Cases[a]			Unselected Cases[b]		
			BinaryDocRes		Percentage	BinaryDocRes		Percentage
	Observed		.00	1.00	Correct	.00	1.00	Correct
Step 1	BinaryDocRes	.00	9564	0	100.0	42032	2324	94.8
		1.00	2748	0	.0	9812	9	.1
	Overall Percentage				77.7			77.6

a. Selected cases Årmåned EQ 2

b. Unselected cases Årmåned NE 2

c. The cut value is ,500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Delta	.036	.007	25.782	1	.000	1.037
	urban(1)	.218	.056	15.139	1	.000	1.244
	less_centralized(1)	-.071	.091	.615	1	.433	.931
	least_centralized(1)	-.229	.082	7.896	1	.005	.795
	AP1(1)	-.155	.058	7.071	1	.008	.856
	VAP(1)	-.019	.065	.085	1	.771	.981
	DAP(1)	.044	.093	.217	1	.641	1.045
	OTHER(1)	-.348	.128	7.443	1	.006	.706
	antiacid(1)	1.257	.055	513.447	1	.000	3.516
	antidepressants(1)	.716	.057	160.369	1	.000	2.047

	Constant	-1.966	.107	335.701	1	.000	.140

a. Variable(s) entered on step 1: Delta, urban, less_centralized, least_centralized, AP1, VAP, DAP, OTHER, antiacid, antidepressants.

3. Output for binary logistic regression for the **year 2008** only. Baseline: smaller urban Boots pharmacy, reservation level for statins.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	363.313	10	.000
	Block	363.313	10	.000
	Model	363.313	10	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	9413.897[a]	.027	.052

Classification Table[c]

			Predicted					
			Selected Cases[a]			Unselected Cases[b]		
			BinaryDocRes		Percentage	BinaryDocRes		Percentage
	Observed		.00	1.00	Correct	.00	1.00	Correct
Step 1	BinaryDocRes	.00	11754	0	100.0	42166	0	100.0
		1.00	1597	0	.0	10972	0	.0
	Overall Percentage				88.0			79.4

a. Selected cases Årmåned EQ 3

b. Unselected cases Årmåned NE 3

c. The cut value is ,500

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Delta	.000	.000	38.878	1	.000	1.000
	urban(1)	.193	.069	7.871	1	.005	1.212
	less_centralized(1)	-.208	.114	3.351	1	.067	.812
	least_centralized(1)	-.271	.100	7.337	1	.007	.762
	AP1(1)	.344	.072	23.102	1	.000	1.411
	VAP(1)	.050	.080	.394	1	.530	1.052
	DAP(1)	-.176	.136	1.677	1	.195	.838
	OTHER(1)	-.163	.152	1.145	1	.285	.850
	antiacid(1)	-.303	.067	20.606	1	.000	.739
	antidepressants(1)	-.492	.069	50.901	1	.000	.612
	Constant	-2.192	.130	286.589	1	.000	.112

a. Variable(s) entered on step 1: Delta, urban, less_centralized, least_centralized, AP1, VAP, DAP, OTHER, antiacid, antidepressants.

4. Output for binary logistic regression for the **year 2009** only. Baseline: smaller urban Boots pharmacy, reservation level for statins.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	1535.392	10	.000
	Block	1535.392	10	.000
	Model	1535.392	10	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	12049.661[a]	.105	.168

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

Classification Table[c]

Observed			Predicted					
			Selected Cases[a]			Unselected Cases[b]		
			BinaryDocRes		Percentage	BinaryDocRes		Percentage
			.00	1.00	Correct	.00	1.00	Correct
Step 1	BinaryDocRes	.00	11232	0	100.0	42688	0	100.0
		1.00	2665	0	.0	9904	0	.0
	Overall Percentage				80.8			81.2

a. Selected cases Årmåned EQ 4

b. Unselected cases Årmåned NE 4

c. The cut value is ,500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Delta	-.001	.000	24.798	1	.000	.999
	urban(1)	.300	.059	25.770	1	.000	1.350
	less_centralized(1)	-.054	.094	.333	1	.564	.947
	least_centralized(1)	-.133	.082	2.647	1	.104	.876
	AP1(1)	-.415	.062	45.128	1	.000	.660
	VAP(1)	-.072	.069	1.075	1	.300	.931
	DAP(1)	-.145	.116	1.571	1	.210	.865
	OTHER(1)	-.304	.117	6.790	1	.009	.738
	antiacid(1)	1.707	.055	958.223	1	.000	5.513
	antidepressants(1)	.703	.055	161.997	1	.000	2.020
	Constant	-1.995	.107	347.141	1	.000	.136

a. Variable(s) entered on step 1: Delta, urban, less_centralized, least_centralized, AP1, VAP, DAP, OTHER, antiacid, antidepressants.

5. Output for binary logistic regression for the **year 2010** only. Baseline: smaller urban Boots pharmacy, reservation level for statins.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	1651.652	10	.000
	Block	1651.652	10	.000
	Model	1651.652	10	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	14635.700[a]	.096	.153

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than ,001.

Classification Table[c]

Observed			Predicted					
			Selected Cases[a]			Unselected Cases[b]		
			BinaryDocRes		Percentage	BinaryDocRes		Percentage
			.00	1.00	Correct	.00	1.00	Correct
Step 1	BinaryDocRes	.00	13040	0	100.0	40880	0	100.0
		1.00	3252	0	.0	9317	0	.0
	Overall Percentage				80.0			81.4

a. Selected cases Årmåned EQ 5

b. Unselected cases Årmåned NE 5

c. The cut value is ,500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Delta	-.001	.000	24.898	1	.000	.999
	urban(1)	.139	.052	7.154	1	.007	1.149
	less_centralized(1)	-.251	.087	8.420	1	.004	.778
	least_centralized(1)	-.196	.072	7.482	1	.006	.822
	AP1(1)	-.140	.057	6.082	1	.014	.869
	VAP(1)	-.157	.059	7.104	1	.008	.855
	DAP(1)	-.176	.099	3.134	1	.077	.839
	OTHER(1)	-.106	.098	1.178	1	.278	.899
	antiacid(1)	1.711	.052	1071.697	1	.000	5.535
	antidepressants(1)	.612	.048	163.595	1	.000	1.845
	Constant	-1.947	.093	440.687	1	.000	.143

a. Variable(s) entered on step 1: Delta, urban, less_centralized, least_centralized, AP1, VAP, DAP, OTHER, antiacid, antidepressants.

Appendix 2 Selected substitution groups

ATCcode	ATCname	S.Group number	Substitution group name	DDDq	DDDunit
A02BA02	RANITIDINE	000012	RANITIDIN BRUSETABLETTER 150MG*	0,300	G
A02BA02	RANITIDINE	000013	RANITIDIN TABLETTER 150MG	0,300	G
A02BA02	RANITIDINE	000014	RANITIDIN TABLETTER 300MG	0,300	G
A02BA02	RANITIDINE	000015	RANITIDIN BRUSETABLETTER 300MG	0,300	G
A02BC01	OMEPRAZOLE	000023	OMEPRAZOL TABLETTER 10MG**	20,000	MG
A02BC01	OMEPRAZOLE	000024	OMEPRAZOL TABLETTER 20MG	20,000	MG
A02BC02	PANTOPRAZOLE	001420	PANTOPRAZOL ENTEROTABLETTER 40 MG****	0,040	G
A02BC02	PANTOPRAZOLE	001525	PANTOPRAZOL ENTEROTABLETTER 20 MG****	0,040	G
A02BC03	LANSOPRAZOLE	000028	LANSOPRAZOL ENTEROKAPSLER 30MG***	0,030	G
A02BC03	LANSOPRAZOLE	000938	LANSOPRAZOL ENTEROKAPSLER 15MG***	0,030	G
C10AA01	SIMVASTATIN	000251	SIMVASTATIN TABLETTER 10MG	0,030	G
C10AA01	SIMVASTATIN	000252	SIMVASTATIN TABLETTER 20MG	0,030	G
C10AA01	SIMVASTATIN	000253	SIMVASTATIN TABLETTER 40MG	0,030	G
C10AA01	SIMVASTATIN	000254	SIMVASTATIN TABLETTER 80MG	0,030	G
C10AA03	PRAVASTATIN	000261	PRAVASTATIN TABLETTER 20MG	0,030	G
C10AA03	PRAVASTATIN	000853	PRAVASTATIN TABLETTER 40MG	0,030	G
N06AB04	CITALOPRAM	000656	CITALOPRAM TABLETTER 10MG	0,020	G
N06AB04	CITALOPRAM	000657	CITALOPRAM TABLETTER 20MG	0,020	G
N06AB04	CITALOPRAM	000658	CITALOPRAM TABLETTER 40MG	0,020	G
N06AB05	PAROXETINE	000661	PAROKSETIN TABLETTER 20MG	20,000	MG
N06AB10	ESCITALOPRAM	000671	ESCITALOPRAM TABLETTER 10MG*****	10,000	MG
N06AB10	ESCITALOPRAM	001651	ESCITALOPRAM TABLETTER 5MG*****	10,000	MG
N06AB10	ESCITALOPRAM	001652	ESCITALOPRAM TABLETTER 20MG*****	10,000	MG

*Only original has been available on the market

**Usually prescribed to children

*** Original not available on the market

****Original (Somac) available at stepped price at all pharmacy chains

***** Original (Cipralex) available at stepped price at one of the pharmacy chains in 2010