PhD thesis
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Generic substitution in Swedish Community Pharmacies
*Understanding the influence of a pharmaceutical policy on pharmacy practice*

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Summary

Background
Generic substitution is a commonly used cost-containment strategy meant to control pharmaceutical expenditure without compromising health objectives. It has been shown effective with regard to lowering the price of medicines, but the practice is still debated as it is found to worry and confuse patients and thereby pose a risk to patient safety. This dichotomy indicates that a policy with one aim, to lower the price of medicines, also has other consequences. Generic substitution is performed in community pharmacies and hence it is there that practice is likely to be influenced by it. This thesis will study community pharmacists’ experiences, patients’ trust in interchangeable medicines, and the influence of generic substitution on patient-pharmacist communication in order to bring about greater understanding of the effects on practice that derive from a pharmaceutical policy. This knowledge can provide a foundation on which a new and improved policy can be built.

Objectives
The overall aim of this Ph.D. thesis is to enhance understanding of how the cost-containment strategy of generic substitution has influenced practice in community pharmacies.

The specific aims of the included studies are as follows:
1. To explore the attitudes and experiences regarding generic medicines and generic substitution among community pharmacists (paper I)
2. To investigate the content of the pharmacist-patient communication in community pharmacy and the influence of generic substitution on dialogue (papers II and III)
3. To assess and analyze how prior experiences, information from pharmacist or doctor, confusion after receiving a generic substitution, view on financial savings, acceptance of generic substitution and socio-demographic factors are associated with patients’ trust in the safety and efficacy of interchangeable medicines (paper IV).

Methods
Semi-structured interviews were used to explore community pharmacists’ experiences and attitudes about generic drugs and generic substitution. The content of pharmacist-patient communication and its influence from generic substitution were investigated through non-participant observations including audio recordings and short-structured questionnaires. Finally, a quantitative questionnaire survey was carried out to study which factors, including
information from the pharmacist, are associated with patient trust in the bioequivalence of substitutable products.

**Results**
The results are summarized for each research question.

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**Pharmacists’ attitude to and experience with generic substitution**
Although pharmacists acknowledge the financial savings of generic substitution, they worry about patients’ ability to handle the switchover. The pharmacists moreover claimed that generic substitution shifts the focus of patient-pharmacist communication from medicinal content to cost and regulations.

**Pharmacist-patient communication and the influence of generic substitution on content**
The findings in paper I contributed to the formulation of the research questions in papers II and III. The results show that very little time is spent talking about medicinal issues during dispensing in community pharmacies, irrespective of whether generic substitution is offered or not. After adjustment for number of prescriptions and socio-demographics, more time is spent communicating about non-medical issues during encounters involving generic substitution. The encounter is not, however, longer in total, nor is more time spent on medical issues.

**Patients’ trust in interchangeable medicines and factors of importance**
Factors seen to significantly increase the odds of a low level of trust in bioequivalence were change in effect or occurrence of side effects whether positive or negative, lower level of education, female gender, and the opinion that changes in drug name and appearance make adherence more complicated. Trust in individual and societal financial savings from generic substitution, and information from doctor and pharmacist were associated with a high level of trust.

**Conclusion**
The results of this thesis indicate that although pharmacists consider generic substitution to shift the focus of communication with patients from pharmaceutical counseling towards cost and regulations, actual pharmacist-patient dialogue contains little medical communication whether or not generic substitution is involved. Moreover, the results showed that more than
one-third of patients claimed that generic substitution complicates adherence. This is associated with a low level of trust in bioequivalence and confirms pharmacists’ experience that generic substitution introduces challenges with regard to patient safety and adherence. And although pharmacists emphasized the challenge generic substitution presents to patients, they do not seem to spend more time talking about medical issues when generic substitution is involved. This indicates that pharmacists need to further embrace the importance of their role in promoting the rational use of medicines and assuring patient safety. Moreover, patients’ experiences with a change in effect or side effect after generic substitution are associated with a low level of trust in bioequivalence, irrespective of whether the change was positive or negative.
Resumé på dansk (Danish summary)

Baggrund
Generisk substitution er en hyppig anvendt cost-containment strategi til at bremse udgifter til medicin uden at gå på kompromis med folkesundheden. Generisk substitution har vist sig effektiv i form af at reducere priser men er stadig omdiskuteret idet det er fundet at føre til bekymringer og forvirring hos patienter og dermed udgøre en risiko for patientsikkerheden. Dette indikerer at en politik med et formål, at reducere medicinudgifter, også kan have andre konsekvenser. Generisk substitution bliver udført på primærapoteker og apotekspraksis vil derfor sandsynligvis blive influeret heraf. Denne afhandling vil undersøge apoteksfarmaceuters erfaringer med, patienters tillid til ligestillede lægemidler og generis substitution indflydelse på patient-farmaceut kommunikation nærmere, for at øge forståelsen af en ny lægemiddelpolitis afledte effekter på praksis. En sådan viden kan forme fundamentet, på hvilken en ny og forbedret politik kan bygges.

Formål
Det overordnede formål med denne ph.d.-afhandling er at øge forståelsen for hvordan cost-containment-strategien generis substitution har influeret på praksisser på primærapoteker.

De specifikke mål med de inkluderede studier er:
1. At undersøge apoteksfarmaceuters holdninger til og erfaringer med generisk medicin og generis substitution (artikel 1)
2. At undersøge indholdet af farmaceut-patient kommunikation på apotek og hvordan generisk substitution influerer på denne dialog (artikel 2 og 3)
3. At vurdere og analysere hvordan tidligere erfaring, information fra farmaceut eller læge, forvirring efter at have modtaget et generisk substitution præparat, syn på økonomisk besparelse, accept af generisk substitution og socio-demografiske faktorer er associeret med patienters tillid til sikkerhed og effekt af ligestillede lægemidler (artikel 4)

Metoder
Apoteksfarmaceuters erfaringer med og holdninger til generiske lægemidler og generisk substitution blev undersøgt gennem brug af semi-strukturerede interviews. Indholdet af
patient-farmaceut kommunikation samt hvordan denne er influeret af generisk substitution blev undersøgt gennem udførelse af ikke-deltager observationer samt auditive optagelser og korte strukturerede spørgeskemaer. Slutteligt blev et kvantitativt spørgeskema uddelt for at undersøge hvilke faktorer inklusiv information fra farmaceuter, der er associeret med patienters tillid til bio-ækvivalente substituerbare præparater.

**Resultater**

Resultaterne er opsummeret i henhold til hvert forskningsspørgsmål.

*Farmaceuters holdninger til og erfaringer med generisk substitution*

Farmaceuter fandt at de økonomiske besparelser grundet generisk substitution var positive men var bekymrede for patienters evne til at håndtere skift af lægemidler. Farmaceuterne var af den opfattelse at generisk substitution flyttede fokus i kommunikationen væk fra lægemiddelfagligt indhold og i stedet over på økonomi og regler.

*Farmaceut-patient kommunikation og generisk substitution indflydelse på dialogen*

Resultaterne i artikel 1 bidrog til formuleringen af forskningsspørgsmålene til artikel 2 og 3. Resultaterne viser her at kun lidt tid bliver brugt i kommunikationen på lægemiddelfaglige forhold, når der udleveres medicin på apotek, uafhængigt om der bliver tilbudt generisk substitution eller ej. Efter at have korrigeret for antal recepter samt socio-demografiske faktorer, blev det fundet at skrankesamtaler der inkluderer generisk substitution bruger mere tid på ikke lægemiddelfaglige forhold end skrankesamtaler der ikke indeholder generisk substitution. Samtaler med generisk substitution er dog samlet set ikke længere og bruger heller ikke mere tid på lægemiddelfaglige forhold.

*Patienters tillid til ligegyldige lægemidler og faktorer med indflydelse herpå*

Følgende faktorer blev fundet associeret med lav tillid: oplevet ændring i effekt eller bivirkninger – positive eller negative, lavt uddannelsesniveau, kvinde samt holdningen at skift i navn og udseende vanskeliggør adherence. Der var større sandsynlighed for høj tillid ved følgende faktorer: opfattelsen af at generisk substitution sparer penge både for den enkelte samt samfundet samt at have modtaget information om generisk substitution fra læge eller farmaceut.
**Konklusion**

Resultaterne fra denne afhandling indikerer, at selvom apoteksfarmaceuter opfatter, at generisk substitution flytter fokus i kommunikationen med patienten fra lægemiddelfaglige forhold til økonomi og regler, så består den aktuelle farmaceut-patient kommunikation kun i begrenset omfang af medicinsk indhold uafhængigt om generisk substitution bliver tilbudt eller ej. Herudover er det blevet eftervist, at mere end en tredjedel af de involverede patienter mener at generisk substitution vanskeliggør adherence. Dette er associeret med lav tillid til bio-ækvivalens og bekræfter farmaceuters erfaringer med, at generisk substitution er forbundet med udfordringer med hensyn til patientsikkerhed og adherence. Selvom farmaceuterne understregede de udfordringer som generisk substitution påfører patienterne, synes de ikke at bruge mere tid på at kommunikere om lægemiddelfaglige forhold, når de udfører generisk substitution. Dette indikerer, at farmaceuter i endnu højre grad bør anerkende vigtigheden af deres rolle i at sikre rationel brug af lægemidler herunder patientsikkerhed. Endvidere er erfaringer omkring ændret (positiv eller negativ) effekt eller bivirkninger efter generisk substitution associeret med lav tillid til bio-ækvivalens.
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### Key concepts and abbreviations

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<tr>
<td>Bioequivalent</td>
<td>A medicine with the same qualitative and quantitative composition in active substances, same dosage form, and same route of administration as the reference drug, with bioavailability demonstrated by appropriate studies (1).</td>
</tr>
<tr>
<td>Brand name medicine</td>
<td>In this thesis a brand name medicine is defined as the first approved pharmaceutical that contains a certain active substance.</td>
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<tr>
<td>Generic medicine</td>
<td>A medicine with the same qualitative and quantitative composition in active substances, same dosage form, and same route of administration as the reference drug (2).</td>
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<tr>
<td>Generic substitution</td>
<td>A cost-containment strategy that gives the pharmacist the obligation or opportunity to substitute prescribed medicine with a bioequivalent product at a lower price.</td>
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<tr>
<td>Health policy</td>
<td>“Decisions, plans, and actions that are undertaken to achieve specific healthcare goals within a society” (3).</td>
</tr>
<tr>
<td>Interchangeable medicines</td>
<td>In this thesis the concept of interchangeable medicines is used to describe two or more medicines with the same active substance in the same amount that are proven to be bioequivalent and therefore can be substituted for one another through generic substitution.</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>In Sweden there are two pharmacy degrees: one three year university degree for prescriptionists, and one five year degree for pharmacists. In community pharmacies and in the case of medicine dispensing are their legal rights and obligations the same. Hence will both professions be defined as pharmacists in this thesis.</td>
</tr>
<tr>
<td>Pharmacy Policy</td>
<td>A policy with the objective to assure availability, quality and rational use of medicines (4).</td>
</tr>
<tr>
<td>Preferred product of the month</td>
<td>“The product that pharmacies should offer to patients the pharmacies have to substitute medicines exposed to generic competition” (5)</td>
</tr>
<tr>
<td>Rational use of medicine</td>
<td>“The rational use of medicine requires that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time and at the lowest cost to them and their community” (6)</td>
</tr>
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1. Introduction

Research and development in recent decades have resulted in treatment options and new effective medicines that promote better health and increase life expectancy. So while we are healthier and live longer, we also use more medicines. As a result, pharmaceutical expenditure has been rising steadily in most European countries since 1990(7). Moreover, it is estimated that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly(8-10). Incorrect use of medicines has serious implications that can cause suffering for the individual(11) and waste society’s resources(10). The increasing cost of pharmaceuticals has thus been a common target of pharmaceutical policies for the last 20 years(12).

Generic substitution is one of the most commonly used pharmaceutical cost-containment strategies, aimed at stimulating competition on the off-patent market and thereby reducing costs without compromising health objectives(7). Mandatory generic substitution was implemented in Sweden in 2002(13). The reform has proven effective, and today Sweden has among the lowest prices of off-patent medicines in Europe(14, 15). However, generic substitution is still debated, as it is found to worry and confuse patients and thus pose a risk to patient safety(16-20).

When generic substitution is implemented, pharmaceutical policy meets practice and the patient at the community pharmacy. It is community pharmacists who alongside their dispensing functions are tasked with providing individualized information and ensuring that patients know how to use their medicines(21, 22). The importance of supporting patients in their use of medicines has become increasingly obvious, as there has been no evidence of a reduction in non-adherence among patients with prescriptions(8, 9) for the past 50 years(9). Generic substitution introduces an extra layer of complexity in the use of medicines in the form of changing colors and names, for example. Moreover, the bioequivalence between interchangeable medicines has been questioned, as patients experience side effects and less efficacy from treatment(16, 17, 23).

It is imperative that pharmaceutical policies are understood, discussed and debated if we are to learn from successes and failures. A greater understanding of the mechanism inherent in a
pharmaceutical policy provides a foundation on which a new and improved policy can be built(24).

A policy with one aim, to lower the price of medicines, also has other consequences. When a reform complicates some patients’ ability to be adherent, it could be assumed that the information and support provided during substitution are essential. Although a high substitution rate is a desirable goal for policymakers (and taxpayers) in order to encourage competition on the pharmaceutical market and lower the cost of medicines, it is only a desirable goal if patients trust the medicine they have just bought at the pharmacy. Therefore the studies in this thesis will focus on how generic substitution has influenced pharmacy practice by exploring community pharmacists’ experiences, as well as the content of pharmacist-patient communication and its correlation with generic substitution, and factors of importance to patients’ trust in the bioequivalence of interchangeable medicines.

Hopefully the results will provide knowledge that will bring more effective interventions and changes in regulations leading to generic substitution that is more optimal for the individual patient and for society.


2. Project objectives

The overall aim of this Ph.D. thesis is to enhance the understanding of how the cost-containment strategy of generic substitution has influenced practice in community pharmacies.

The specific aims of the included studies are as follows:

1. To explore the attitudes and experiences regarding generic medicines and generic substitution among community pharmacists (paper I)

2. To investigate the content of the pharmacist-patient communication in community pharmacy and the influence of generic substitution on dialogue (papers II and III)
   - By analyzing the content and time allocation of the patient-pharmacist communication in pharmacies, and
   - The relationship between the extent and content of patient-pharmacist communication in community pharmacies and generic substitution in relation to other variables earlier found relevant for communication: number of prescriptions, and socio-demographic factors.

3. To assess and analyze how prior experiences, information from pharmacist or doctor, confusion after receiving a generic substitution, view of financial savings, acceptance of generic substitution and socio-demographic factors are associated with patients’ trust in the safety and efficacy of interchangeable medicines (paper IV)
3. BACKGROUND

This thesis aims to investigate how a pharmaceutical policy and cost-containment strategy with one aim, to reduce the costs of medicines, influences pharmacy practice. In this section on background, the concept of pharmaceutical policy and the framework of generic substitution and its role on an imperfect market are described. Pharmacy practice and the role community pharmacies and pharmacists play in today’s healthcare system are then presented. Finally, the current knowledge of the influence of generic substitution from the perspective of healthcare professionals and patients is summarized.

3.1. Pharmaceutical policy

Pharmaceuticals play a key role in the prevention and treatment of disease(24). The worldwide availability of effective, safe and affordable pharmaceuticals is a key challenge for the global governance system(12, 25). Large economic interests are at stake within the field of pharmaceuticals. At the same time, consumers (patients) are unable to judge the quality, safety and, in many cases, the efficacy of the medicine, as well as whether the price is reasonable. They depend on others to assure a solid process of evaluation and approval of pharmaceuticals. As a consequence, pharmaceutical markets are more highly regulated than most other markets(12). The rationale of regulation is to meet health policy objectives, i.e. to protect public health, make safe and efficacious medicines available and ensure quality of care without excessive expenditure(12, 25).

3.1.1. Definition of pharmaceutical policy

Pharmaceutical policy can be seen as a set of principles based on politics, values, ideology and evidence that guide decision-making(24). The WHO further describes national pharmaceutical policy as a guide for action as well as a commitment to a goal(4). Policy expresses and prioritizes goals set by the government for the pharmaceutical sector. Policy should also contain the main strategies for how to attain the goals set. In general, the objective of a national pharmaceutical policy is to assure the availability, quality and rational use of medicines(4).
3.1.2. Rational use of medicines

Rational use of medicines as part of pharmaceutical policy reaches beyond technical involvement with medicinal products and their development and into the area of behavior. The WHO defines the rational use of medicines as follows: “The rational use of medicines requires that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time and at the lowest cost to them and their community”(6). Irrational use includes non-adherence to dosing regimens, failure to prescribe in accordance with clinical guidelines and inappropriate self-medication, for example. Ensuring rational use of medicines should involve a positive effort to promote and identify those uses of medicines that will provide the greatest benefit and the lowest risk(25).

Over half of all medicines are prescribed, dispensed or sold inappropriately according to estimations by the WHO(10). Moreover half of all patients fail to take them correctly(8-10). The incorrect use of medicines has serious implications and can cause suffering for the individual(11) and result in a huge waste of resources(10). For a policy to be successful, it must therefore also be based on the promotion and maintenance of understanding as well as support for the thinking that underlies that specific policy. Information and education are important complementary processes to this end(25).

3.1.3. Cost-containment as part of pharmaceutical policy

Pharmaceutical policy is sometimes described as a branch of health policy, which the WHO defines as “decisions, plans, and actions that are undertaken to achieve specific healthcare goals within a society”(3). However, although many of the actors involved are the same, the presence of the pharmaceutical industry in the pharmaceutical arena makes the study and understanding of the pharmaceutical field different from healthcare(24). New drug development is valuable to society as it leads to improvements in health outcomes. However, claims from the industry regarding constraint on profits that threaten valuable innovation must be critically reviewed and the promotion of a major industry balanced with effective and efficient spending on pharmaceuticals(25). To prevent the cost of pharmaceuticals from increasing, governments can employ pharmaceutical policies in the form of cost-containment strategies(7). Cost-containment is seldom the main pharmaceutical policy objective, but rather one of the tools employed to make the best use of limited resources to increase public health(12). Cost-containment strategies commonly include price and profit controls in the
pharmaceutical distribution chain, expenditure control, and measures targeted at physicians, pharmacists and patients(7, 26).

3.2. Using generic substitution to address increasing costs of pharmaceuticals
As new and more sophisticated pharmaceuticals have been developed, public spending on pharmaceuticals has risen steadily among most European Union (EU) members and OECD countries the past 40 years(7, 27, 28). Reasons for increased expenditure include the introduction of new and often more expensive medicines, aging populations in developed countries, more preventive treatment of conditions previously left untreated, availability of medicines for diseases previously not treatable, and increased use of lifestyle medicines(25, 26, 29). The increased expenditure on and prices of pharmaceuticals are also greatly affected by the imperfections in the demand and supply of pharmaceuticals, which leads to market failure(30). One of the most commonly used strategies to prevent the cost of pharmaceuticals from increasing is generic substitution. In 2010 generic substitution was mandatory in seven, indicative in 15 and disallowed in five countries in the EU(7).

3.2.1. The rationale of generic substitution
Generic substitution is a cost-containment strategy meant to contain pharmaceutical expenditure without compromising health objectives(7). In practical terms, generic substitution means that prescribed medicine is substituted by a cheaper medicine with the same qualitative and quantitative composition in active substances, same dosage form, and same route of administration as the reference drug, with bioavailability demonstrated by appropriate studies(1, 2, 31, 32). Generic substitution encourage competition in the off-patent market, thereby reducing prices and pharmaceutical expenditure(33).

3.2.2. The impact of generic substitutions on the pharmaceutical market
The first approved pharmaceutical containing a certain active substance is known as a brand name drug. New drugs, like other products, are developed under patent protection, which gives the company the sole right to sell the product(12, 25). Patent protection together with brand loyalty and length of regulatory approval contribute to imperfections in the supply side of the pharmaceutical market(12).
Patent rights allow originator companies to charge a price often 10 or 20 times higher than when the patent expires(25). After patent expiration the barrier to entry is removed and generic equivalents of the original brand can be produced and manufactured(12). The characteristics of the market that arise when patents expire create a potential for competition. As generic manufacturers do not incur research and development costs, they are able to offer significantly lower prices, see figure 1. Hence, generic medicines are thought to provide a solution to overstretched pharmaceutical budgets(34). Still, there is a standard assumption that the price competition in pharmaceutical markets is weak(12). By introducing generic substitution, the competition on the off-patent market increases due to the increased market share provided to the bioequivalent product with the lowest price. Increased market share and sales motivate companies to offer the lowest price and hence the price-level decreases(35). Generic producers currently dominate pharmaceutical markets in volume of units sold, while originators dominate values in sales(25). In 2014 all off patent-medicines (including both generics and off-patent brands) accounted for 92% of all prescription volume in Europe, although they only represent 47% of the value(36).

In theory, generic equivalents are close to perfect substitutes for the original brand and are thereby expected to compete on price. Some loyalty to the original brand could theoretically remain after patent expiration, but has not been found to limit off-patent competition(12). However, the off-patent market also differs from the patent market on the demand side, since to a greater extent products are selected on the basis of cost awareness due to financial incentives for physicians, pharmacists and patients alike(12, 34). Doctors can have an impact on the use of generics through generic prescribing as well as by allowing or disallowing generic substitution. In cases where pharmacists allow or disallow the additional effects of generic substitution, they also can influence the actual market share accorded to the product.

Figure 1. Cost in SEK per defined daily dose (DDD) in the Stockholm municipality the months before and after patent expiration of Omeprazole, Simvastatin and Citalopram (Source: Stockholm Läns Landsting 2015).
with the lowest price, and the overall use of generics. Moreover, the information and recommendation provided by physicians and pharmacists have been found to influence patients’ acceptance of generic substitution(16, 37, 38).

3.3. Generic substitution in community pharmacies
Dispensing pharmacists in community pharmacies undertake the substitution of prescribed medicine with a cheaper bioequivalent product. This means that generic substitution policy meets practice and patient for the first time at the community pharmacy. While the impact of cost containment policies on quality of care is often unclear(12), the importance of evaluating pharmaceutical policies has become increasingly apparent(39). The effect of generic substitution on the price level of off-patent medicines is well known from international economic evaluations(14). However, a pharmaceutical policy with the sole aim of lowering the cost of medicines is also likely to influence the practice of where it is performed, i.e. pharmacy practice. In order to study the influence of generic substitution on practice, the history and concept of pharmacy practice need to be introduced.

3.3.1. The concept of pharmacy practice
Pharmacy has previously been defined as “the art, practice, or profession of preparing, preserving, compounding, and dispensing medical drugs”(40). Its foundation has traditionally been rooted in the natural sciences, with focus on pharmaceuticals and technical skills for their preparation. However, over the past 60 years, three of four mainstays (drug preparation, preservation and compounding) have been lost to the industry. The focus of the pharmacist profession has thereby switched from that of compounder and dispenser to that of a “drug therapy manager”(8). Left as part of pharmacy practice is the task of dispensing. In its broadest sense, this task is an important part of the healthcare system performed by the pharmacist as part of a healthcare team. In its narrowest sense, dispensing can be approached as marketing and sales(41). The aim of pharmacy practice as defined by the International Pharmaceutical Federation and WHO is “to contribute to health improvement and to help patients with health problems to make the best use of their medicines”(21).
3.3.2. The pharmacist’s role in achieving rational use of medicines

When global challenges – fair access to safe, efficient and affordable medicines, and their rational use – are addressed, profound changes in the healthcare delivery system follow. As a consequence, a paradigm shift is taking place within pharmacy practice, with the result that the role of the pharmacist needs to be redefined and reoriented(28). In addition to the technical aspects of pharmaceutical services, the scope of pharmacy practice now also includes patient-centered care. Some describe the heart of pharmacy practice, especially in community pharmacies, as the patient-pharmacist interaction(42). This requires a switch from more “medication-centered” or “task-centered” tasks to a patient-centered practice, including expanded pharmacy services(8). In this new format, it is no longer enough to simply provide medication in the safest and most efficient manner. Alongside dispensing, pharmacists working in community pharmacies shall provide information about medicines and their use, and must therefore master all cognitive functions of counseling(21, 22). The importance of supporting patients in their use of medicines has become increasingly obvious as it is estimated that half of the patients with prescriptions and regular access to essential medicines fail to take them correctly(8, 9), with no evidence of any substantial change over the past 50 years(9).

3.3.3. Pharmaceutical counseling at community pharmacies

In the practice of their profession, pharmacists have the potential to improve patients’ quality of life and therapeutic outcome and are the healthcare professionals most accessible to the public(43).

All Nordic countries have legal requirements regarding the content of the counseling in community pharmacies, with the main focus on the use of medication(22). The requirements for counseling at community pharmacies are also described in several professional guidelines, national and international(21, 44-46). While guidelines published by professional organizations in the USA and Australia provide detailed instructions on which information to include, the guidelines issued by the International Pharmacist Federation as well as the local Swedish guidelines are more general. However, all agree that the pharmacist shall provide sufficient specific information on health, disease and medicine so that patients understand how to use their medicine as described in their treatment plan or prescription(21, 44-47).

As the more patient-oriented role developed, so did the concept of pharmaceutical care and pharmaceutical care services. Cipolle et al. define pharmaceutical care as “a patient-centered
practice in which the practitioner assumes responsibility for a patient’s drug-related needs and is held accountable for the commitment”(48). The concept of pharmaceutical care introduced a more systematic approach to identifying, preventing or resolving drug therapy problems. When different pharmaceutical care services are performed in community pharmacies, the target groups are often patients with a specific health conditions such as asthma(49, 50), cardiovascular diseases(51, 52), diabetes(53) or with a more complex medication regime(54).

Pharmaceutical counseling services in community pharmacies have been shown to improve adherence(55) and to have a positive effect on treatment outcomes, e.g. better glycemic control in people with type II diabetes(56). Pharmaceutical care services at community pharmacies have moreover been found to enhance patient empowerment and make patients feel safer about their medications(57).

### 3.3.4. Patient-pharmacist communication during dispensing of medicines

All patients collecting prescribed medicines in community pharmacies shall receive information about their medicines and how to use them. Efficient, motivating, and purposive communication is a very important tool in the meeting with the patient(58). The communication process serves two primary functions. First, it establishes the ongoing relationship between the pharmacist and the patient. Second, it provides the necessary exchange of information to allow an assessment of patients’ health conditions, decisions to be made regarding treatment plans and their implementation, and an evaluation of the effects of treatment on patients’ quality of life(58). However, studies in both Europe and the US have found that pharmacies provide little information(59-61). A review of the literature from 2009 concludes that the proportion of patients who receive pharmaceutical counseling when collecting medicines at the pharmacy varies greatly(62). One reason is the method used to measure the occurrence of counseling and another is the type of prescription. Lower counseling rates were seen in observational and patient-oriented studies and higher counseling rates for patients with new compared to regular prescriptions(62).

A participatory approach has been found to result in significantly longer pharmacist-patient interactions(63). Other factors identified as influencing the degree of interaction with patients during dispensing include age of patient(64), age of pharmacist(65), gender(64), time of the day(64), busyness of the pharmacy(66) therapeutic class(62, 65), first or repeat
The introduction of generic substitution added new requirements to pharmacist-patient communication. When a substitution is available, the dispensing pharmacist must inform patients about the substitution and their right to decline it(13). This requirement is likely to have influenced pharmacist-patient communication during dispensing as well as the pharmacist’s practice.

3.4. Previous findings regarding the influence of generic substitution on practice

Studies analyzing how generic substitution has influenced practice have most often focused on the perception, attitudes and experiences of healthcare professionals and their practice, as well as on patients and their use of medicines. Although the substitution of brand name pharmaceuticals at community pharmacies is common practice in countries worldwide, it is still met with skepticism by some healthcare professionals and patients. The outcome and
experiences with generic substitution are associated with a wide range of factors that will be described in the following sections; some are illustrated in figure 2.

3.4.1. Healthcare professionals’ perspective
In general, physicians and pharmacists acknowledge the cost-savings due to generic medicines as well as their role in improving access to treatment worldwide(69). Studies on healthcare professionals’ experience with generic substitution show mixed findings. A majority of Swedish physicians have been found positive about generic substitution(70, 71). However, when the strategy was introduced in Denmark, a small study found that the majority of Danish physicians were dissatisfied with the system and wanted to abolish it on the grounds that it was incomprehensible, added to their workload and they didn’t have enough information about it(72). Overall a recent review study concluded that about one in four physicians had negative perceptions of generic medicines and thought that they caused more side effects(73). A Finnish study found that more than half of the physicians thought interchangeable medicines in certain medicine groups were not equally effective and safe(37). In contrast, a qualitative study conducted in Melbourne found that some physicians viewed generics as equally effective, although none of the respondents was aware of the requirements for bioequivalence of generic drugs(74). This confirms other findings of misconceptions or a low level of knowledge among physicians regarding the requirements for interchangeable generics(75). Slovenian physicians also considered generics to be the bioequivalent of brand medicines, although 16% stated that the pharmaceutical industry had tremendous impact on their prescribing, and one out of four said that they would only increase their generic prescribing if additional clinical trials were presented(76). A study among Italian pediatricians showed that only 13.5% have prescribed generics for more than half of their patients, even though the majority of the physicians considered generics to have sufficient or good efficacy(77).

Studies of pharmacists’ perception of generic substitution found the majority positive(71, 78, 79). Gill et al compared attitudes in Finland, Italy and Australia and found that pharmacists considered it a professional challenge to convince customers about the bioequivalence of generics(80). A review study concluded that a high proportion of pharmacists had negative perceptions about generic medicines, with more than 30% considering generics to be inferior in quality compared to branded medication(73). However, few had negative perceptions about
substituting generic alternatives for brand name drugs. Overall, pharmacists have been found to have better knowledge of the concept of bioequivalence than physicians(69). Good communication between patients and healthcare providers has been identified as one vital aspect of reducing patients’ anxiety about generic substitution. It also motivates and educates them, thereby minimizing the risk of double medication, for example, and increasing adherence to treatment(16, 81).

3.4.2. Patients’ perspective

Studies on how patients have been influenced by generic substitution have found that the exchange confuses and worries patients, possibly leading to mix-ups and non-adherence(16, 18-20, 82). Findings regarding the actual impact on patients’ adherence are, however, inconclusive, showing both increased and decreased adherence(82-84). Patients experiencing their first time substitution have been found at higher risk of non-persistence(19). Patients’ perceptions of the received product and trust in interchangeable medicines have been found important for adherence, received effect and side effects(85-87). This is in line with previous findings showing that patients’ medication beliefs explain a great deal of non-adherence(88). Grégorie et al. has moreover established that patients’ perceived benefits of a drug treatment may predict persistence with said treatment(89).

Overall, the majority of the Swedish, Norwegian and Finnish patients reported that they were positive about generic substitution(16, 18, 23, 37). Danish patients who experienced a generic substitution do not have more concerns about their medicine than those who had no experience with generic substitution(90). One-third of the patients in two Norwegian studies were negative about generics or reported negative experiences after generic substitution(16, 82). The main reasons for worry about generic substitution were fear of side effects and uncertainties about the similarity of the drugs(82). Heikkilä et al. found that a large number of patients were confused or uncertain when they answered questions about the effectiveness and safety of interchangeable medicines(91). The change in appearance of the medicine has been found to worry patients(81, 92) and increase the risk of medication errors(20). A Swedish study found that 7.5 % of the patients participating reported using their medicine incorrectly due to generic substitution(18). Similar results were found some years later where 6.8% of the Swedish patients stated that they had used their medicines incorrectly due to substitution, and
40% reported at least one difficulty related to substitution. Most frequently reported were perceived lack of efficacy, a different safety profile and general confusion(23).

Past experience with cheaper medicines, secondary or lower education, low income and living area were all significantly associated with an increased willingness to choose generics(93). Patients’ understanding of the substitution has been found correlated with level of education and information from the physician(94). Moreover, the information and recommendations from and perceptions of physicians and pharmacists are found to influence patients’ perception of generic substitution as well as acceptance of the exchange(16, 37, 38, 82, 94-96). Anxiety reduction was most effective when the advice of the pharmacist was directly in keeping with that of the physician(16). Several studies conclude that the information and recommendations from physicians and pharmacists influence patients’ experiences with and acceptance of the substitution.

### 3.5. The Swedish study setting

The Swedish healthcare system is tax-funded. The Ministry of Health and Social Affairs is responsible for health and medical care (including pharmaceuticals), public health, social services, elderly care, financial support for families, pensions, sickness insurance, disabilities, housing, construction and religious communities(97). The Medical Product Agency Sweden (MPA) is responsible for approving pharmaceuticals as well as the regulation and surveillance of the manufacture and sale of pharmaceutical products(98).

#### 3.5.1. Reimbursement of pharmaceuticals

The degree of reimbursement for pharmaceuticals increases with patients’ expenses for prescription medicines included in the pharmaceutical benefits scheme (PBS)(33). When patients’ cost of medicines included in the PBS reach SEK 2200 within a period of 12 months, all exceeding costs are subsidized by the government until the end of the 12-month period. Patients with chronic conditions normally receive a prescription valid for one year at a time, and are dispensed medicine to cover 90 days of treatment at a time.
3.5.2. Generic substitution in pharmacies

In Sweden, the governmental costs for pharmaceuticals increased on average 5% per year during the 1990s (99). Mandatory generic substitution was introduced in Sweden in 2002 to reduce increasing costs (13). The new policy resulted in an extensive number of price reductions for pharmaceuticals without patent protection. From October 2002 to December 2003, the average price for drug substances without a patent decreased by 27%, whereas the price for drug substances with a patent remained unchanged (100). According to an estimation from 2006, the accumulated savings from the introduction of the reform between October 2002 and December 2005 was SEK 7 billion (101). Today Sweden has among the lowest prices for off-patent pharmaceuticals eligible for generic substitution in Europe (14, 15).

Based on clinical data provided by the manufacturing pharmaceutical companies, the MPA decides which pharmaceuticals with the same amount of active substance and the same formula are to be considered bioequivalent and thereby exchangeable (2, 31). The Dental and Pharmaceutical Benefits Agency (TLV) appoints which interchangeable product (included in the PBS) for each package-size group of products with generic competition has the lowest price. This is referred to as the preferred product of the month (and part of the so-called PV-system). As indicated by the name, the interchangeable medicine with the lowest price is appointed for one month at a time (35), meaning that the product offered to patients can vary from one month to the next. Swedish community pharmacists shall offer the preferred product of the month to all patients with a prescribed medicine included in the PBS for which there is a cheaper interchangeable alternative. The substitution can be opposed by doctors for medical reasons such as allergy. The pharmacist can also oppose the substitution if it gives rise to patient concerns due to individual medical needs, complications in relation to poly-pharmacy or packaging issues, for example. The patient can also choose to decline the substitution, but will then have to pay the price difference between the prescribed medicine and the cheapest interchangeable product (13). Pharmacies are compensated by 11.50 SEK extra for dispensing products included in the PV-system (102).

Prior to 2009, Sweden had a state-owned pharmacy monopoly. This monopoly was abolished by the Medicine Distribution Act (103), and 2/3 of all pharmacies were sold to private actors (103). The goal of the liberalization of ownership was to increase availability (referring to number of pharmacies and opening hours) and increased entrepreneurship (104, 105). Due to the liberalization of pharmacy ownership, new regulations regarding the already mandatory
generic substitution were introduced. These regulations aimed at preventing increases in pharmaceutical prices by limiting the pharmacies’ flexibility as to which product to dispense. Prior to liberalization, the interchangeable product with the lowest price available at the pharmacy could be dispensed. According to the new regulation, the product that TLV appointed as the cheapest alternative should be provided to all patients within 24 hours.

3.5.3. Regulations on information and counseling in pharmacies.

All community pharmacies in Sweden are obligated to provide individualized information and counseling about pharmaceuticals and how to use them correctly(103). Counseling is only allowed to be given by staff with a proper pharmacy education(103); pharmacy technicians (1.5 year post high-school degree) can give counseling about OTC-medicines and pharmacists can counsel patients about OTC medicines and prescription medicines. Pharmacists shall, when dispensing a prescribed medicine, give the patient accurate and attentive care(106). Moreover, as far as possible, they should assure that patients know how to use their medicines when leaving the pharmacy(47). Since the implementation of generic substitution, pharmacies are also obligated to inform the patient where a generic substitution is available, about the substitution and the patient’s right to decline it(13).
4. METHODS

The focus of this thesis is to understand the influence of a pharmaceutical policy, generic substitution, on pharmacy practice. Four studies were conducted in total, see figure 3. Study I explored community pharmacists’ experiences and attitudes about generic drugs and generic substitution through semi-structured interviews. The findings in study I contributed to the formulation of the research questions in studies II and III, which investigated the content of pharmacist-patient communication and how it was influenced by generic substitution; methods were non-participant observations (audio-recordings) and short, structured interviews. Study IV, a quantitative questionnaire survey, assessed which factors, including information from the pharmacist, are associated with patient trust in the bioequivalence of substitutable products.

Figure 3. Overview of papers I-IV.

Methods were chosen on the basis of the complexity and formulation of each research question. Further, a combination of qualitative and quantitative methods was considered an advantage, as collecting diverse types of data provides the best understanding of a research problem(107). Table 1 presents an overview of the study designs and methods.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study design</th>
<th>Study population</th>
<th>Data collection instruments</th>
<th>Analysis</th>
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<tbody>
<tr>
<td>1</td>
<td>Semi-structured interviews</td>
<td>Pharmacists (n=16) working at community pharmacies (n=5)</td>
<td>Interview guide</td>
<td>Qualitative analysis: Content analysis - Identifying units, condensation of meaning units (no predetermined categories) into themes and sub-themes. Consensus analysis</td>
</tr>
<tr>
<td>2</td>
<td>Observations with audio recordings</td>
<td>Pharmacy customers (n=282), pharmacists (n=29) working at community pharmacies (n=6)</td>
<td>Audio recordings, unstructured observation protocol</td>
<td>Qualitative analysis: Content analysis - identifying units, condensation of meaning units into themes (predetermined) and sub-themes. Consensus analysis. Inter-rator reliability test (Cohen’s kappa)</td>
</tr>
<tr>
<td>3</td>
<td>Observations with audio recordings, structured interviews</td>
<td>Pharmacy customers (n=282), pharmacists (n=29) working at community pharmacies (n=6)</td>
<td>Audio recordings, unstructured observation protocol, structured questionnaire: socio-demographics</td>
<td>Quantitative analysis: Descriptive statistics, bivariable analyses, two types of regression analyses (odds ratio and linear)</td>
</tr>
<tr>
<td>4</td>
<td>Questionnaire survey</td>
<td>Customers (n=719) at community pharmacies (n=12)</td>
<td>Questionnaire: Socio-demographics, trust in bioequivalent pharmaceuticals, counseling, prior experiences with generic substitution financial gain, confusion</td>
<td>Quantitative analysis: bivariable statistics, univariable analyses, regression analyses (odds ratio)</td>
</tr>
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</table>

Table 1. Methodological overview of the four studies.
4.1. Pharmacists’ experiences with and attitudes to generic drugs and generic substitution (paper 1)

In the first study, the pharmacists’ perception of generic substitution was explored through semi-structured interviews. The study population of community pharmacists was chosen for two reasons: first, pharmacists are the healthcare professionals who perform the substitution and experience its influence on their own practice, the dispensing procedure, and the patient every day. Second, at the time of the study, the pharmacists’ perspective had not been studied in any of the Nordic countries. A qualitative exploratory approach with semi-structured face-to-face interviews was used, because qualitative studies are considered the most appropriate for studying patterns and processes in people’s thoughts and behavior(39). This approach allowed us to gain answers to “how” and “why” questions, which is highly relevant in this case, with very little known about the influence of GS on the practice of community pharmacists.

Sampling procedures

For both pharmacies and pharmacists, the invitation to participate in the study was based on purposeful sampling aimed at heterogeneity. The choice of purposeful sampling was based on interest in gaining broad knowledge of the topic by including pharmacists with atypical experiences in order to understand the entire range of experiences with and breadth of generic drugs and generic substitution(39). Pharmacies located in large and small municipalities were asked to participate, and consideration was given to pharmacy profile, geographic distribution, size and surrounding environment. Five out of six pharmacies agreed to participate, with one declining on the grounds of heavy workload. All of the pharmacists working in the selected pharmacies were invited to participate. Respondent recruitment aimed for heterogeneity with regard to gender, years of work experience, education level (including both prescriptionists, who have a three-year university degree in pharmacy, and pharmacists, who have a five-year university degree in pharmacy) and age. Years of work experience have previously been found to correlate with understanding the substitution system(108).

Workload, work schedule and availability of pharmacists were determining factors for the number of pharmacists interviewed at each pharmacy. As redundancy was the primary criterion, pharmacies and interviews were recruited until saturation, i.e. when no new information was forthcoming from new interviews(109-111).
Data collection
The data for study 1 were collected by semi-structured interviews. An interview guide was
developed, containing topics and suggested questions(112) based on findings from previous
research(16, 78), and tested in a pilot interview(113). The pilot interview did not result in any
changes in the interview guide, which covered the following themes: attitudes about generic
drugs and generic substitution, knowledge regarding generic substitution, received
information and potential measures. Most of the questions were open ended. Examples of
questions: In your opinion, what are the advantages/disadvantages of generic substitution?
What do you think of generic drugs? What kind of training or information have you received
about generic substitution? Probing was used to expand on responses. All interviews were
audio recorded.

Data analysis
All interviews were transcribed verbatim from audio recordings prior to analysis. The
transcripts were read repeatedly, key words and phrases were extracted, compared and
combined to form categories. Categories were then combined into main themes. The
categories were derived inductively, i.e. no categories or themes were predetermined.
Inductive category development allows the formulation of categories in terms of and as close
as possible to the material(109, 114). The coding process was initiated by both authors coding
three interviews together. The subsequent part of coding was done by the first author, and
then audited and discussed with the second author. During the final section of the analysis, as
both authors had gained a deeper understanding of the data, categories were rearranged,
renamed, divided if containing different types of data, and merged if they overlapped to
assure that the final categories were exhaustive and consistent, but mutually exclusive(109,
113, 115, 116). The differences that arose were discussed until consensus was reached. The
authors have different disciplinary backgrounds and therefore different perspectives, as the
first author is a pharmacist and the second a social scientist. Multiple coding, especially when
coders have different disciplinary backgrounds and interests, is considered a strength, as the
content of disagreements resolved by consensus discussions can yield new insights into
refining coding frames(117).
4.2. The content of the patient-pharmacist communication in community pharmacies and the influence of generic substitution on dialogue (papers II and III)

In the second and third studies, communication during dispensing in community pharmacies was studied, as well as the influence of generic substitutions on communication content and disposition of time. This focus was chosen for two reasons. First, the results of the first study showed that pharmacists consider that generic substitution shifts the focus in the dialogue towards non-medical issues when they would rather discuss medical issues, possibly resulting in the omission of important medical information. Whether the content of the dialogue had actually been influenced by generic substitution was, however, unclear. Second, to the best of my knowledge, no one had studied whether generic substitution, among other factors, had actually influenced communication, and few had studied the overall content of Swedish dispensing dialogue. The two earlier Swedish studies on pharmacist-patient communication had only included information about the questions asked or information provided by the pharmacists(65), or had a small sample size and were conducted more than 10 years ago(118), after which major changes likely to influence pharmacy practice have occurred(119). As in theory the role of the pharmacist has become more patient-centered(8, 42), it was considered relevant to determine how big a part of overall dialogue was spent in practice on medical vs non-medical issues, before assessing the influence of generic substitution. Audio-recorded observation was chosen due to its directness, and because data can be gathered as events occur rather than relying on what is reported to have happened(39, 113). Short-structured interviews were chosen as a complement for acquiring information about socio-demographics and previous experiences of the patients.

Sample selection

In the interests of achieving a representative sample, i.e. a sample that reflects the diversity of counseling settings and environments in Swedish community pharmacies(39), six community pharmacies were selected on the basis of size of municipality, geographic location, size of pharmacy, pharmacy ownership, surrounding environment and socioeconomic status of area. Although one pharmacy declined to participate, another pharmacy with a similar profile was invited and agreed to participate. All of the pharmacists working at the six community pharmacies during the period of data collection were informed about the study and invited to participate. Patients visiting the pharmacy to collect prescribed medicines for themselves were approached consecutively. Data were collected at different times of day and all days of the
week including weekends in order to include a variety of patients collecting prescribed medication.

**Data collection**
Data were collected through observations with audio recordings and short-structured interviews. Observers used an observation protocol to write down activities that occurred during dispensing but could not be registered audibly, for instance, if there was a third person waiting beside the patient. In addition, a short-structured interview guide was developed with questions about age, gender, education level, country of birth and previous experiences with generic substitution. A data collection strategy was also established and piloted in twenty-three observations to achieve a high degree of standardization, i.e. to assure that all respondents were informed, invited to participate and observed in the same way(7).

Three people collected data. The first author, who conducted the pilot observations and established the data collecting procedure, instructed the other observers on their first day at each pharmacy. Patients who chose to participate were interviewed before or after their medicines had been dispensed. The observer followed the patient and placed a recorder on the counter and then walked away, so that the conversation between pharmacist and patient could take place in private. The observer followed the conversation visually from a distance to register events not covered by the audio recording.

**Data analysis**
The dispensing encounter and all verbal communication between patient and pharmacist were audio recorded. Two main categories were predetermined based on the findings of the first study: medical issues and non-medical issues. One-third of the observations was transcribed verbatim for the initial part of the categorization where the preliminary subcategories were determined. The recordings were listened to and transcripts read multiple times, with the units and themes identified combined into preliminary subcategories(120). All subcategories were inductively derived, allowing the formation of categories as close as possible to the material(109, 114). The categories and any uncertainties or ambiguities regarding classification were discussed among the three coders during a total of six meetings, until consensus was reached and the categories established. When changes or specifications were made in the definition of the subcategories during the coding process, all observations were recoded to match any changes(114). All consultations were listened to at least twice during
the quantitative coding procedure and categorized with regard to time spent on each category and occurrence of categories in the communication. Silence longer than three seconds was also registered.

Only the communication between patient and dispensing pharmacist was coded. However, communication was also coded in situations where a second pharmacist participated in the dispensing to answer questions.

Inter-rater reliability with regard to how the content was categorized was measured using Cohen’s kappa (121). Fifteen observations, two or three from each pharmacy, were coded by all three coders and Cohen’s kappa calculated, resulting in the following kappa values: rator A and B $\kappa = 0.90$, rator B and C $\kappa = 0.89$, rator A and C $\kappa = 0.87$, indicating very good strength of agreement between the coders.

The result of the categorization in study II was analyzed using descriptive statistics, presenting seconds spent per category as well as time spent in silence. In study III, the result of the categorization was combined with the data from the short questionnaire mostly covering socio-demographics. Six explanatory variables were included in the analysis: patients’ gender, age, country of birth, education level, number of prescriptions the patient wished to collect ("number of medicines"), and occurrence of generic substitution; see table 2.

**Table 2. Overview of outcome and explanatory variables in study II.**

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>Explanatory variables</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time of encounter</td>
<td>Occurrence of generic substitution*</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Time spent on medical issues</td>
<td>Number of prescriptions</td>
<td>0, 1, 2, 3, 4, 5, 6+</td>
</tr>
<tr>
<td>Time spent on non-medical issues</td>
<td>Socio-demographic variables</td>
<td></td>
</tr>
<tr>
<td>Occurrence of generic substitution*</td>
<td>• Age</td>
<td>&lt;20, 21-40, 41-60, 60+</td>
</tr>
<tr>
<td></td>
<td>• Country of birth</td>
<td>Sweden, Other</td>
</tr>
<tr>
<td></td>
<td>• Education level (highest level finished)</td>
<td>Elementary School, High School, University</td>
</tr>
<tr>
<td></td>
<td>• Gender</td>
<td>Male, Female</td>
</tr>
</tbody>
</table>

* Applied as outcome in logistic regression analyses and as explanatory variable in bivariate and linear regression analyses
The “number of medicines” was determined by listening to the audio recordings, and reflects the number of medicines the patient wanted to collect for which he or she had a prescription, irrespective of whether the medicines were available at the pharmacy. Patients with six or more medicines were merged into one group due to few observations with more than six medicines. Occurrence of generic substitution was defined based on the communication in the audio recordings, as when generic substitution was offered to the patient, or when a pharmacist substituted the medicine without informing the patient of the option to accept or deny. Some encounters were excluded due to incomplete interviews (n=28).

The bivariable-association between time spent on each category and the explanatory variables (socio-demographic characteristics, number of medicines, generic substitution) was assessed by time categories: total time, time spent on medical issues, time spent on non-medical issues. The median value and range corresponding to the 10th and 90th percentile were calculated for each group of the explanatory variables. Spearman’s Rho was calculated for the linear relationship between number of prescriptions dispensed (1-6+) and each of the three time measures.

Two different multivariable analyses were applied to study 1) which of the studied factors that was associated with greater odd of being offered a generic substitution and 2) how the studied factors co-varied with the content of the pharmacist-patient communication. Odds ratio was calculated for occurrence of generic substitution according to socio-demographic characteristics and number of products (95% confidence interval). Linear regression was used to test predictors for time spent on different categories, applying number of products as the primary explanatory variable and socio-demographic characteristics (dummy variables) as co-variables. T-tests and robust standard errors were applied to test the null-hypothesis of no linear correlation (95% CI). The four age categories were merged into three due to few observations in the youngest age group. Individuals with missing values on education (n=1), number of prescriptions (N=20) and with no valid prescription (n=4) were excluded from the multivariable analyses.
4.3. Factors associated with patients’ trust in bioequivalence of interchangeable medicines (paper IV)

The fourth study underlying this thesis, a questionnaire survey among medicine users, aimed to assess how prior experiences, information from pharmacist or doctor, confusion after generic substitution, view on financial savings, acceptance of generic substitution and socio-demographic factors are associated with patients’ high or low level of trust in the safety and efficacy of interchangeable medicines. The scale used to measure patients trust was previously developed by Rathe et al(122).

Questionnaire development

A questionnaire was developed based on previous findings regarding factors relevant to patients’ trust in and acceptance of generic substitution(19, 81, 123, 124). The questionnaire included three different sections and questions regarding socio-demographics. Section 1 consisted of views on generic medicine, a scale developed by Rathe et al(125), and questions regarding acceptance of generic substitution. The scale measured patients’ trust in equivalence (safety, quality and effect), with a high score meaning low trust (max =5) and a low score high trust (min=1). In this article, we reversed coding so that a high score means high trust, since it increases the understanding of the results. Section two consisted of eight items concerning patients’ prior experiences with generic substitution, and information regarding generic substitution from physicians and pharmacists. Section three included five items regarding difficulties with changes in color/name, and attitudes to financial savings due to generic substitution. All items were answered on a 5-point Likert response scale. Two different Likert scales were used: 1= Strongly agree to 5=Strongly disagree and 1=Always to 5= Never. The questionnaire also asked for socio-demographic data (age, gender, education level, native language, income, number of medicines taken daily, type of medicine).

The questionnaire was initially tested for content validity by two senior researchers with many years of experience in quantitative and qualitative method development and one researcher with in-depth knowledge of the field. A total of 20 cognitive interviews with concurrent and retrospective "thinking aloud" and probing were conducted with focus on comprehensibility, appearance and relevance(126). Some changes were made to the questionnaire after the pilot. The new version was shown to the pilot respondents who approved of the changes. The feasibility of the established data collecting procedure and comprehensibility of the final questionnaire was piloted a second time over two days at two different community
pharmacies. A total of 41 questionnaires were handed out to pharmacy customers who met inclusion criteria. Minor post-pilot modifications were made to the order of questions and the layout.

**Sample selection**

All of the municipalities in Sweden were divided into 10 strata based on average yearly household income. Household income has previously been found to influence patients’ preference for generic substitution(124). One municipality was chosen in each stratum with the aim of achieving a representative sample with regard to number of inhabitants in each municipality, geographic distribution, and number of people born outside Sweden. For strata with more than 20% of the population, two municipalities were chosen resulting in a total of 12 municipalities. One pharmacy in each municipality was chosen for its representativeness with regard to placement (urban/rural), surroundings (hospital, shopping mall, city center, suburb, isolated), pharmacy owner and size of pharmacy. A total of 12 pharmacies were invited to participate and all agreed. Proportionate sampling was used in regard to number of questionnaires being collected in each strata, the aim being that the numbers in the group selected for the sample reflect the relative numbers of the population as a whole(113).

**Data collection**

Customers at the selected pharmacies were approached consecutively. Swedish-speaking customers who had previously used prescribed medicines and had been offered a generic substitution were invited to participate in the survey. Before handing out the questionnaire, the data collectors clarified the concept of generic substitution for all customers and requested their informed consent. Some customers (n=160) wanted the data collectors to read the questions to them due to poor eyesight, for example. Aiming at representivity, we collected data during March and April 2015 at various times and days of the week to include all types of customers. All weekday opening hours were covered. Data were also collected over two weekends. Having a data collector present allows respondents to sort out questions regarding the questionnaire(127).

**Data analysis**

For the analysis, trust in generic substitution was dichotomized (low≤3, and high>3) and applied as the outcome variable. The bivariable association between trust and the potential explanatory variables gender, age, education level, native language, income, number of
pharmaceuticals per day, prior experience of with changes in effect/side effects, information received (physician or pharmacist), opinions regarding generic substitution making adherence more complicated and trust in lowered individual and societal costs for medicine was assessed, see tables 1 and 2. The data for the four items regarding prior experiences were dichotomized into groups of “never experienced” and “have experienced”. The two items regarding information from the physician were merged into one item “information from the doctor”, and the data dichotomized into groups of “have received information” and “have never received information”. The same procedure was followed for the two items regarding information from the pharmacist. In addition, these data were combined into two new items: “received information from both the pharmacist and the doctor” and “have never received any information”. The data for these items were dichotomized into “yes” and “no”. The data from the five items regarding confusion and financial aspects were also dichotomized, with “strongly agree/agree” in one group and “neutral/disagree/strongly disagree” in another; see table 2, paper IV.

To analyze the association between low trust and each of the explanatory variables (gender, age, education level, income, native language, number of pharmaceuticals taken daily, acceptance of generic substitution, prior experience with changes in effect/side effects, information received, confusion and financial aspects), crude odds ratios (OR) with 95% confidence intervals (CI) were estimated using univariable (simple) logistic regression. Information received from pharmacist was excluded because nearly all (99.2%) respondents had received information at some point.

4.4. Ethical considerations

The ethical review board of Uppsala, Sweden did not consider ethical approval necessary for any of the four sub-studies. However they issued official recommendations regarding confidentiality for sub-studies 2, 3 and 4. All requirements were met: informed consent was received from all respondents before data collection was initiated, participation was voluntary and data confidentiality ensured.
5. Results

This thesis explores four research questions and presents the results from the studies in four papers, which are included as appendices I to IV. The results of each study will be summarized in this section.

5.1. Pharmacists’ attitudes to and experiences with generic drugs and generic substitution (paper I)

All respondents acknowledged the pros and cons of generic substitution, and had both positive and negative opinions. They stated that generic substitution had affected their daily work as well as dispensing and patients’ use of medicines in a variety of ways. The analysis resulted in three main themes and twelve sub-categories; see table 3 in paper I.

The role of the pharmacist in generic substitution

The pharmacists acknowledged the importance of communicating with patients in order to make them feel safe and motivated to take their prescribed medicine/s. Building trust by maintaining a neutral position with regard to generic substitution was considered important. Some pharmacists expressed concern about exposing patients to potential risks, especially those patients with allergies.

Another key concern was that with the introduction of generic substitution, the content of patient-pharmacist communication was perceived as more focused on finances, generic substitution, equivalence, packaging and excipients than on treatment. The respondents would have preferred communication about the medication, strengthening and clarifying the prescribers aim, and making sure that the patient realized the importance of adherence. Many respondents further stated that it would be optimal if the prescriber informed the patient about the substitution. Pharmacists also mentioned more non-fruitful discussions and more time-consuming storage and administrative work as important consequences. Many respondents found discussing substitution aggravating, tiring and demanding.

Most respondents could not recall having received any information or training about the new legislation/policy or on how to communicate with patients about generic substitution. Some had received information about how to handle substitution in their IT systems. Several wished for guidelines and information about generic substitution and how to discuss substitution with patients.
Pharmacists’ concerns about patients

A main concern of many pharmacists was that patients had not understood substitution and had hence mixed up their medicines, possibly resulting in double medication or disruption of treatment. Most pharmacists recalled encountering a double prescription situation or disruption of drug use or patients not daring to take the “new drug”. Patients using antipsychotics were considered to react negatively to the switch. Furthermore, the elderly were pointed out as an especially vulnerable group, since they more often had multiple prescriptions and thus a wide range of changing names, colors and shapes to keep track of.

Respondents suggested that cost savings were possibly at the expense of patients’ quality of life and health. They pointed out that generic substitution can be extremely demanding for patients who are afraid of side effects or do not feel well on the substituted drug. However, they further stated that most patients do not comment on the substitution or react negatively, but rather consider the lower cost as positive.

Suggestions for potential measures to optimize generic substitution were generic prescribing, identical packaging and tablets for interchangeable drugs, more information from the physician, increased cooperation between the pharmacist and the physician, an upper limit to number of generic drugs for each brand drug, and an upper age limit for being offered generic substitution.

The generic drug

Respondents pointed out that generic substitution lowers the price of medicines, which is an advantage for both society and patients by lowering society’s cost for pharmaceuticals and facilitating treatment for patients with lower incomes. The respondents stated that the lowered cost saves money that can be better used in the healthcare system.

Most of the pharmacists considered generic drugs equivalent to and as effective as their reference medicinal product, and they stated that they trust decisions from the authorities. However, several respondents said that since many patients return with accounts of finding differences in effect they become insecure about the bioequivalence of generic drugs. Generic drugs were often thought of as being inferior to brand medicines by the respondents with regard to coating and packaging.
Some respondents stated that reports of side effects or non-effects were seldom passed on to authorities due to lack of time or inadequate information. The introduction of generic drugs on the pharmaceutical market was identified as a threat to medical research and the future development of new medicines.

5.2. Communication in Swedish community pharmacies (paper II)
Six out of six invited pharmacies and 29 pharmacists (27 females) out of 32 accepted participation in the study (90.6% participation rate). A total of 407 patients were approached, out of which 282 agreed to participate (69.3%). Not all gave reasons for turning down the invitation, but the reason most often given was lack of time. Observations that did not comply with the inclusion criteria (n=9), had poor sound quality that affected the ability to hear the conversation (n=2) and incomplete recordings (n=12) were excluded. For the analysis, 259 observations remained. In 174 out of the 259 observations, the patient was a woman.

Patient-pharmacist communication
In addition to the predetermined main categories, medical and non-medical issues, twelve subcategories were identified in the analysis; see table 1 in paper 2. The total time of the dispensing encounter was on average 3 (median) or 3.8 (mean) minutes. Little time, on average 11 (median) or 25 (mean) seconds, was spent talking about medical issues. In 22.4% of the dialogues, there was no communication at all regarding medical issues, and in almost half of the encounters, less than 10 seconds was spent on medical issues; see table 2 in paper II. The subcategory within the main category of medical communication on which most time was spent was “user instructions”, including information about how patients should use and store medicine.

Patients and pharmacists spent on average 72 (median) or 85 (mean) seconds communicating about non-medical issues. Most time was spent on administrative issues related to the prescription, such as the availability of e-prescription, validity of the prescription, and customer requests for a summary of their e-prescriptions. The second largest subcategory called “other non-medical content” included directions to a different part of the pharmacy, and general small talk such as greetings and comments on the weather. A total of 183 (mean) or 112 (median) seconds were spent in silence; see table 1 in paper II.
5.3 The influence of generic substitution on the content of patient-pharmacist communication (paper III)

As described under section 5.2, participation rates were as follows: pharmacies 100% (n=6), pharmacists 90.6% (n=29) and patients 69.3% (n=282). Some observations were excluded due to reasons mentioned in 5.2. In addition, observations lacking complete interviews (n=28) were excluded for this study, resulting in 231 observations. Population characteristics and the number of prescriptions patients wished to collect are described in table 2, paper 3. Less than one-third of the dispensing encounters involved generic substitution.

The bivariate association between time spent on each category for all socio-demographic characteristics, occurrence of generic substitution and number of prescriptions is presented in table 3, paper III. The median total time increased with number of prescriptions and age of patient, and decreased with length of education. Dispensing encounters involving generic substitution were longer (244 vs 167 seconds), and more time was spent on non-medical issues. A larger number of prescriptions were associated with the same trends: longer encounters and more non-medical communication. The total time of the dispensing encounter ranged from 34 to 1206 seconds (just over 20 minutes), time spent on non-medical issues from 10 to 493 seconds (8.2 minutes) and time spent on non-medical issues from 0 to 283 seconds (4.7 minutes). The odds ratio for generic substitution to occur increased with number of prescriptions (OR=1.85, p<0.001, 95% CI 1.38-2.48); see table 4, paper 3.

Results from the linear regression analysis of increases in time spent (medical, non-medical, total) as function of number of products dispensed (1-6+) are shown in table 5, paper III. Socio-economic variables and occurrence of generic substitution were controlled for in this analysis. Time spent on all categories significantly increased with number of prescriptions and total time of encounter (p<=0.05). In encounters involving generic substitution, more time was spent on non-medical issues (β, 0.32, p=0.01). However, the encounters were not longer in total, nor was more time spent communicating about medical issues. Time spent talking about non-medical issues increased with the age of the patient (age 40-60: β, 0.23, p=0.08, patients 60+: β, 0.055, p<0.001). Time spent on medical issues increased significantly with number of prescriptions. Also, non-significant tendencies of more time spent on medical issues was seen for higher level of education (high school: β, 0.18, p=0.07, university: β, 0.17, p=0.11).
5.4. Factors correlated with patients’ high or low trust in bioequivalence of interchangeable medicines (paper IV)

A total of 12 pharmacies were contacted regarding data collection at or near the pharmacy, and all agreed to participate. Inside or by the entrance to the pharmacies, 849 pharmacy customers who met the inclusion criteria were invited to fill out the questionnaire; 719 agreed to participate giving a response rate of 84.7%. The majority of the participants were women (59.1%), the most common age group was 66-80 years old (44.5%), the most common level of highest education finished was university or equivalent (44.5%), and 93% had Swedish as their native language. Half of the study population was currently using three or more medicines per day.

Patients’ trust in GS (range 1 to 5) was on average 3.75 (median) or 3.73 (mean), see table 1, paper IV. The average trust value was lower among women than men and decreased with increased age and number of pharmaceuticals. Lower trust was seen among respondents with lower education level and lower income, see table 1, paper IV.

The 82.1% of the respondents who sometimes, often or always accepted generic substitution had a trust index of 4 compared to 2.75 among those who seldom or never accepted the substitution. More than half of the respondents with low trust still accepted the substitution in most cases. A total of 29.6% had experienced less effect after substitution and 22.1% more side effects. However, 18.4% had experienced better effect and 14.2% fewer side effects. Almost all respondents (99.2%) had received information about generic substitution from a pharmacist at some point, and 65% from a physician. The trust was slightly higher among patients who had received information from a physician (4.00) compared to those who had not (3.75). Slightly more than one-third of the patients considered the change in appearance to complicate adherence while 40.8% considered changes in name challenging. Few (6.5%) disagreed that generic substitution saves money for society while 68% agreed or agreed strongly. Two-thirds agreed that generic substitution lowered costs for themselves, see table 3, paper IV.

The result from the univariable (simple) logistic regression in the form of odds ratio (OR) for low trust with 95% confidence intervals (CI) is shown in table 3, paper IV. The following groups were found to be significantly associated with increased odds of having low trust: female gender (OR: 1.96, 95 % CI: 1.39-2.76), elementary school as highest education level
(OR: 1.72, 95% CI: 1.14-2.60), seldom or never accepting generic substitution (OR: 12.38, 95% CI: 7.89-19.43) previous experiences of less effect (OR: 11.30, 95% CI: 7.56-16.88), better effect (OR: 2.65, 95% CI: 1.78-3.96), more side effects (OR: 11.22, 95% CI: 7.42-16.96) and fewer side effects (OR: 4.37, 95% CI: 2.18-6.78), the opinion that changes in name (OR: 2.27, 95% CI: 1.63-3.15) or appearance (OR: 1.85, 95% CI: 1.33-2.58) are challenging, and the opinion that the pharmacy profits from GS (OR: 2.08, 95% CI: 1.38-3.13). Having received information from the doctor (OR: 0.71, 95% CI: 0.51-0.98), or from both the doctor and the pharmacist (OR: 0.70, 95% CI: 0.50-0.97) as well as strongly agreeing, agreeing or being neutral to whether GS saves money for me (OR: 0.28, 95% CI: 0.18-0.44) or for society (OR: 0.17, 95% CI: 0.09-0.32) were significantly associated with decreased odds of having low trust, see table 3, paper IV.

5.5. Summary of main findings
The main objective of this thesis, to study the influence of generic substitution on pharmacy practice, was approached through four studies. Pharmacists’ attitudes to and experiences from generic substitution were explored, the content and time disposition of the pharmacist-patient communication and its influence on GS was assessed, and what factors associated with patients’ trust in bioequivalence of interchangeable medicines were studied. The main findings are summarized in figure 4.

**Figure 4. Overview of main findings paper I-IV.**
6. Discussion

The main findings of the four studies will be discussed in this chapter. The overall aim of this thesis is to understand how generic substitution has influenced pharmacy practice. Together and in relation to each other, the results in the four papers provide a fuller picture. Therefore, the findings of the studies and their relation to previous studies and theoretical framework will be discussed together rather than each paper separately. Moreover, methodological strengths and limitations will be discussed.

6.1 Discussion regarding main findings

In this thesis, the influence of generic substitution has been studied from the perspectives of pharmacists and patients. The influence of generic substitution on pharmacist-patient communication was also assessed.

Paper I explored pharmacists’ attitudes to and experiences with generic substitution. The results show that although the respondents acknowledge the financial savings due to generic substitution, they worry about patients’ ability to handle the switchover. The pharmacists moreover claim that generic substitution has shifted the focus of pharmaceutical counseling towards cost and regulations.

The findings in paper I contributed to the formulation of the research questions in papers II and III, which aim at studying pharmacist-patient communication during dispensing in community pharmacies and how it has been influenced by generic substitution. The results show that little time is spent talking about medicinal issues during dispensing in community pharmacies, irrespective of whether generic substitution is being offered or not. In encounters where generic substitution is offered, more time is spent communicating about non-medical issues. However, the encounter is not longer in total, nor is more time spent on non-medical issues.

In paper IV factors of importance for patients’ trust in interchangeable medicines were assessed. The results show that factors seen to significantly increase the odds of low trust in bioequivalence were any change in effect or side effects, positive or negative, confusion about correct medicine use after the substitution, a graduate school degree as the highest level of
education completed and female gender. Trust in the personal and societal financial savings from generic substitution, and information from doctor and pharmacist were significantly associated with decreased odds of low trust.

The overall main findings of these four papers will be discussed below in relation to previous findings and theoretical framework.

6.1.1. Generic substitution’s influence on the pharmacist’s practice (papers I, II and III)

The exploration of the pharmacists’ attitudes to generic medicines and generic substitution in paper I shows that pharmacists worry about patients’ ability to handle the substitution and consider generic substitution to have moved the focus of communication with the patient towards cost and regulations. Several Nordic studies have confirmed that some patients get confused as well as worried after generic substitution (16, 23, 37), which can lead to additional adherence challenges (17, 82). Although the pharmacists in paper I express concerns about patients’ ability to handle the substitution, paper III found that no more time is spent on communication regarding medical issues during dispensing with generic substitution compared to dispensing without. The results indicate that although pharmacists emphasize and worry about the additional challenge generic substitution introduces to patients, they do not provide additional support in the form of spending more time discussing medical issues. This suggests that they have yet to embrace their role as key actors in preventing non-adherence and assuring patient safety, also in relation to generic substitution.

During dispensing encounters where generic substitution is offered, more time is spent, however, on non-medical issues such as practical and administrative information regarding the prescription. Swedish pharmacies are obligated to inform patients about substitution and their right to decline, hence it is likely that more time will be spent on non-medical issues (13). The result in paper I moreover found that pharmacists consider generic substitution to add time-consuming extra work, for instance, more complicated storing. As mentioned in section 3.5.2, Swedish pharmacies are compensated by 11.50 SEK for each interchangeable medicine dispensed as part of the PV-system (102). This governmental compensation was introduced to cover the additional work of handling the administration of multiple generics within each substitution group. This thesis did not investigate how much additional time is spent handling the administrative aspects of generic
substitution. Nonetheless, an increased administrative burden is likely to follow the increased complexity due to the liberalization of Swedish pharmacy ownership and the related revision of the original policy on generic substitution. New and additional pharmacy owners, pharmacies and suppliers are entering the re-regulated pharmacy market, making it larger and more varied (128), see figure 5. Moreover, the number of generic alternatives and the groups eligible for generic substitution are increasing due to patent expirations (25).

**Figure 5.** Overview of essential actors and the flow of information needed to assure the continuous supply of the interchangeable medicines with the lowest price to the patient, i.e. generic substitution.

Pharmacists play an important role in the implementation and development of generic substitution and can affect the outcome (16, 129). Hence changes in generic substitution policy should assure that pharmacists’ incentive to dispense the lower priced generics is maintained (130). Moreover, since community pharmacies are part of the Swedish healthcare system and pharmacists are healthcare professionals, it should also be in their professional interest to contribute to cost-efficient spending of public resources.

Although paper I reports pharmacists’ concerns about patients’ ability to handle substitution, no more time is spent discussing medical issues during dispensing with generic substitution compared to dispensing without (paper III). This suggests that although the pharmacists acknowledge the additional challenges, they do not provide additional support to address them.
To summarize, pharmacists consider substitution to add to their administrative burden. This trend is likely to follow increased market complexity as well as the additional number of generics for each substitution group. The authorities are aware of the problem and have tried to address it through additional compensation.

6.1.2. A patient-centered approach in theory but not in practice? (papers II and III)

Although pharmacists are most certainly healthcare professionals, the results from study II concerning overall pharmacist-patient communication during dispensing show that little or no time is spent on medical issues, confirming earlier findings(59-61). The only factor in paper II found to be associated with more time spent talking about medical issues involved the number of pharmaceuticals. National and international requirements and guidelines regarding counseling in pharmacies confirm the role of the pharmacist as a provider of individualized information and advice to medicine users(21, 44, 46, 47, 103). However, the results of these studies of pharmacists at Swedish community pharmacies indicate that to some extent the pharmacists are unable to comply with legal requirements regarding communication during dispensing of medicines, irrespective of generic substitution(22). The lack of communication regarding medicines indicates that Swedish medicine users do not get as much value from their encounters at the pharmacy as they could. Lack of pharmaceutical counseling could also lead to negative health outcomes for patients. From a professional perspective, the inability to meet work-related obligations could also lead to poor morale among the pharmacists(131).

So why is communication not focused on medical and pharmaceutical issues? Among other factors, the extent of counseling is seen as being influenced by pressure from legislation(66, 132). In Sweden the MPA is responsible for assuring that the legislation regarding information and counseling is followed(103). In a report from TLV, however, the MPA states that it is difficult to assure that the requirements regarding information about prescribed as well as over-the-counter (OTC) medicines are met(133). While the MPA does not have permission to use secret shoppers (also called mystery shoppers), today surveillance is focused on assuring that pharmacy staff continuously update their professional skills through various forms of education. Moreover, dispensing encounters are sporadically followed up during inspections(133). If in line with current legislation, the Swedish government wants pharmacies to help optimize health in the population, surveillance must be adjusted accordingly.
Another explanation could be lack of incentives to focus attention on the quality of pharmaceutical counseling. Remuneration has been identified as a facilitator for the implementation of cognitive services(134). The Swedish system pharmacies are compensated for each package dispensed, meaning that an increase in the selling of medicines and merchandise leads to profit, while providing additional information during dispensing does not(102).

Moreover, the content of communication is likely to be influenced by the patient’s expectations, since a precondition for a meaningful medicine dialogue is that the patient wants to be part of the healthcare provider-patient alliance(135). While traditionally the role of pharmacists has involved compounding and dispensing medicines(41), today the responsibility of community pharmacists is assuring and enhancing the safe and correct use of medicines, and understanding medication-taking behavior, thereby protecting the public against the dangers inherent in their medicine use(21, 41, 58). However, the results of this thesis indicate that patients have not yet acknowledged pharmacists in this role. Previous studies have found that patients’ expectation can vary(136, 137). Some patients want information and consultation when visiting a pharmacy, while others just want to purchase their medicine as quickly as possible(137). Different expectations have also been seen with pharmacists considering their role as providing risk management information, while patients consider their physician to have responsibility for their healthcare(138). In confirmation, Schommer et al. found that patients do not acknowledge the pharmacist as an advisor for medicine, relying instead on the physician to give advice about medicines(139). Pharmacists have also been found to perceive greater benefits from providing pharmaceutical care services than do patients(140, 141).

In summary it can be said that while in theory pharmacists today have a more patient-centered approach as medicine therapy managers, papers II and III show that little medicinal counseling is provided at community pharmacies, irrespective of generic substitution. This is confirmed by other studies and the dearth of medicinal information provided is found associated with pressure from legislation, patients’ expectations and lack of incentives. The limited surveillance of the counseling in Swedish pharmacies does not signal its importance. If community pharmacists are to contribute to the improved use of medicines and high patient
safety, the system for governmental compensation to pharmacies must be formulated in such a way that quality counseling is profitable and encouraged.

6.1.3. Health literacy – an unaddressed part of pharmacy communication (papers II, III and IV)

The results of papers III and IV show that content of communication as well as trust in bioequivalence are associated with the patient’s level of education. More time seems to be spent talking about medical issues with patients who have finished high school or university compared to patients with a lower level of education. Patients with less than a high school education, together with patients over 60 and men, are more likely to be represented among individuals with low health literacy(142). The concept of health literacy is used to describe patients’ ability to understand, gain access to and use health information(143). Additional support in the form of more time spent discussing health information has been shown to be important for this group(144). Although these people need more clarification of information, they are found to ask fewer questions(145, 146), thus depending on healthcare professionals to identify their need for support. Pharmacies are obligated to provide individualized information(103), however the result in paper III show that none of the encounters with these groups included additional communication on medical subjects. On the contrary, the results indicate that dispensing encounters for patients with a higher level of education contain more time spent talking about medical issue. This suggests that the counseling provided during dispensing is more reactive than proactive, influenced by the questions asked by the patient rather than the pharmacist’s evaluation of the patient’s need for information and support.

A lower level of education was found significantly associated with low trust in bioequivalence. Education level have previously been found associated with correct understanding of what generic medicines is, were a correct understanding was less common among patients with a lower level of education(94). Information from physicians also was associated with a higher level of trust, but on a lower level of significance. This suggests that while providing information in general is important, it is also relevant that sufficient time is spent talking to the patient to enable understanding of bioequivalence and the concept of generic substitution.

In summary, the findings of papers II, III and IV show that little medical information is provided, irrespective of socio-demographic characteristics or generic substitution, and that a
low level of trust in bioequivalence is associated with a lower level of education. This group of patients is overrepresented among individuals with low health literacy, who often need support in the form of more time spent discussing medical issues. This suggests that lack of information and sparse medical counseling could negatively impact the patients with the greatest need, especially when generic substitution is involved.

6.1.4. The relevance of trust in efficacy and safety for full effect after generic substitution (papers I and IV)

The findings in paper IV show that about 70% of responding patients trust in the bioequivalence of interchangeable medicines. The scale used to measure trust was developed and previously used in Denmark(122). When applying the same dichotomization as Rathe et al, 80% of the Swedish patients had trust in bioequivalence, compared to 90.44% of Danish patients(122). In Finland, a study showed that 88.4% of patients held the opinion that cheaper generics are effective(91). This indicates that Swedish patients have a lower level of trust in the equivalence of generic medicines. Study I moreover found that while many patients return with accounts of finding differences in effect some pharmacist also state to become insecure about the bioequivalence of generic drugs.

Patients’ perceptions of the received product and trust in the bioequivalence of exchangeable products (generics and brand medicines) have been found crucial for adherence, received effect and side effects(85-87). Overall, outcome in relation to expectations is often discussed as placebo or nocebo effects. The powerful effect of placebo treatment is demonstrated in numerous studies(147), and maximizing placebo effects and minimizing nocebo effects have been stated as an important part of healthcare professionals’ job(148).

The packaging and name of medicines have been found to influence patients’ outcome of treatment where the same effect was received for a placebo marked as the original brand and the actual pharmaceutical marked as a placebo(86). This confirms previous findings where changes in labeling from branded to generic have been found associated with reduced objective and subjective measures of medication effectiveness and increased side effects(87). Since placebo effects are part of the overall effect from treatment, placebos should not replace treatment(148). Increasing positive information was found to boost the effect of both placebo and treatment(86). Pharmacists doubting the quality, as indicated by paper I confirming
previous studies(73), is likely to affect the information provided to the patient and could in the end also influence the outcome(86). The placebo effect as well as nocebo effects are important aspects of receiving the full benefit from treatment, which needs to be considered also in the case of generic substitution. The information provided to patients is an important component of care and could influence the outcome(86).

### 6.1.5. Managing changes in effect and side effects after generic substitution while maintaining market competition (papers I and IV)

In paper IV about 30% of the Swedish patients report having experienced less effect from their medication after a substitution, and almost every fourth patient reports more side effects, confirming indications about patients reporting change in outcome from paper I. Despite the rigid requirements regarding the demonstration of bioequivalence in order to be eligible for generic substitution(1, 2, 31), other studies confirm that patients report changes in effect and/or side effects after substitution(16, 23, 81, 82). However, the results of paper IV also show that about one in five patients has experienced a better effect after the substitution and 14% report fewer side effects. Any change in effect or side effects, positive or negative, was seen to significantly increase the odds of low trust in bioequivalence. Since the data in study IV were collected at one point in time, it is impossible to determine causality, i.e. if prior experiences led to low trust or if patients with low trust experience changes in effect and side effects to a greater extent. While patients’ trust in the efficacy of interchangeable medicines has been found important for adherence, effect from treatment and side effects(85-87), it is likely that a personal experience of different treatment outcome after a substitution is likely to result in doubts regarding equality.

It has previously been stated that in many cases consumers (patients) are unable to judge the efficacy of their medicine and thus depend on others to assure a solid process of evaluation and approval of pharmaceuticals(12). Patients receiving information about generic substitution from a doctor are significantly more likely to have a high degree of trust in interchangeable medicines, confirming previous findings(16, 37, 38). Pharmacists in the first study underlying this thesis said that even though patients report side effects or changes in effect, this information is seldom passed on to the MPA, although required by law(149), due to lack of time or insufficient information. All suspected side effects, confirmed or not, must be reported to the MPA as soon as possible according to legislation(149). Determining
whether there is an actual change in effect or side effect, and whether it is due to generic substitution can be difficult, but is not grounds for not reporting the event. Moreover, in cases where the effect cannot be determined objectively by a test, as in the case of pain management, depression, anxiety and many other conditions, the only outcome measure is the effect and improvement in health experienced by the patient.

In Sweden, physicians have the option of refusing substitution for medical reasons such as side effects due to allergy or hypersensitivity(13). However, resources available for healthcare and medicines are limited. Many “no” responses to substitution from doctors not only directly increase the cost of medicines, but could also affect prices due to a reduction in the market share for the preferred product of the month (described more fully in section 3.5.2). The mechanism here is that prices could rise if it becomes less desirable for manufacturers of interchangeable medicines to compete on price to become “product of the month”(35). The best choice for the individual patient and for society must therefore always be weighed in order to achieve a fair and cost-efficient healthcare system.

6.2. Methodological discussions
All four papers underlying this thesis have measured an outcome at one point in time (cross-sectional data). Hence is it not possible to establish causality but only association between variables(150).

The results from study 1 provide knowledge regarding Swedish community pharmacists’ perspective and experiences with generic substitution. The study also has some limitations. Few men were included in the study, even though heterogeneity was strived for. However, very few men work in Swedish community pharmacies(151), a pattern also found at the five pharmacies participating in the study. It cannot be ruled out that saturation was not reached in this aspect, since men could have different views. Moreover, the interviews were conducted at the respondents’ workplace, which could have influenced the respondents. On the other hand, the interviews were conducted in private and in an environment familiar to respondents, which could have helped them feel more comfortable(152). One of the authors performing the analysis was a pharmacist, which could have affected her analysis of the results. She had, however, not worked with dispensing of medicines during the time of the analysis. The data were also analyzed by the second author with a background in social sciences, adding another
perspective to the analysis and hopefully counterbalancing the risk of bias(115, 117). Having more than one coder is generally considered a strength, as consensus discussions can yield new insights and refine the coding scheme(117).

The study design of papers II and III had two primary strengths. First, the use of audio-recordings of the communication to provide a more direct and unbiased material than for instance interviews or questionnaire were respondents are asked about which information that was received or given(39, 113). Second, the combination of qualitative and quantitative data and analysis to provide a more complete understanding of the content of the communication as well as the association between communication and generic substitution.

Some limitations should also be noted. First, the observer effect is an inherent part of observation studies, i.e. participants are aware of being observed and therefore may change their behavior(113). The change of behavior is thought to be for the better, hence it could be hypothesized that since the observers came from the university, pharmacists would enhance their pharmaceutical counseling. This would mean that less time is spent communicating about medical issues in the real world compared to the encounters in the study. Alternatively, the pharmacists could have avoided providing pharmaceutical counseling out of fear of giving the wrong advice, resulting in less counseling than normal. Moreover, patients may have refrained from asking questions due to the recording device. However, all participants received information about anonymity before the data collection began and the observer stepped away from the counter after placing the recorder, so that the encounter could take place in privacy. As another measure to overcome the observer effect, the observer stayed at each pharmacy for several days (approximately one week at each pharmacy) in order for the pharmacists to grow accustomed to the situation(113). Second, because observation is a labor-intensive method requiring the presence of the observer, the number of settings is often limited(39). For this reason, few pharmacies were included in this study. In the interests of achieving a representative sample, i.e. a sample that reflects the diversity of counseling settings and environments in Swedish community pharmacies(39), pharmacies of different size were selected in municipalities of different size and geographic location, with different owners and varied surrounding environment and socioeconomic status of area. The patients invited to participate were approached consecutively. However, data were collected during different times of the day and different days of the week in order to include different types of customers. Compared to the group of medicine users in Sweden, the study population had an
overrepresentation of women, people with a university education, and people above the age of 60. While there was a non-significant tendency that encounters with patients having a higher level of education this could mean that the seen time spent on medical issues is slightly overestimated compared to the real average time. Moreover, patient age was divided into large groups, which makes it hard to uncover any real differences with regard to age groups. Hence it cannot be ruled out that the participants and their dispensing encounters differ from the dispensing encounters of medicine users on the whole. Lastly, given the study design, it is hard to make a non-response analysis of the content of the communication. The most common reason for patients to decline participation in the study was lack of time. Since patients in a hurry might want fast dispensing, this could indicate that the dispensing encounters in the study are longer than they might have been had non-respondents also been included.

The method used in paper IV had two primary strengths. First, since questionnaires were handed out by a data collector according to a predetermined procedure, all respondents received the same information and were able to ask questions if any uncertainties arose with regards to the questions. Second, a high response rate (84.7%) was achieved, which increased the validity of the results. There are also some limitations to this study. Due to the labor-intensive method of having data collectors hand out the questionnaires, the number of pharmacies where data were collected was quite low. To have a representative sample, all municipalities in Sweden were stratified into 10 strata based on level of income for the household. One or two municipalities in each stratum and a pharmacy in each municipality were chosen. Proportionate sampling with regard to the number of questionnaires collected in each stratum was the aim in order to reflect the population as a whole(113). The degree to which this number of interviews was reached varied, however. With regard to gender distribution, the number of men and women in the study population represents the population of (prescription) medicines users in Sweden, as well as the whole Swedish population. With regard to age, there was an underrepresentation of young medicine users. No data regarding income and education level are available for the group medicine users. However, when comparing with the Swedish population (most of whom have used prescription medicine at some point), there was an underrepresentation of people with the lowest income level, and an overrepresentation of people with the second-lowest income level. People with an education higher than high school were also overrepresented in the material. Since the results indicate that respondents with a lower level of income are underrepresented, this could have influenced the results, so that the trust levels are actually lower that the one found in paper IV.
The customers who declined to participate represented the study population as well as the population *medicine users* with regard to gender distribution. Based on the age estimated by the data collector, the largest number of declines to participate were received from patients between the ages of 51-65 and 65-80, but overall that was in proportion to the general age distribution in the study population. This information should, however, be interpreted with great caution, since the actual age of the people who declined to participate is not known.

There were also some questions with lower response rates or a high number of “neutral” responses, which could indicate that the question was hard to understand or did not feel relevant to the respondent. A majority of the non-responses were due to the item in question not being applicable to the respondent, such as questions regarding change in effect for patients who had never agreed to generic substitution. However, in particular the item regarding pharmacies’ profit received a large number of neutral responses, which could be an indication of uncertainty or no strong opinions on the subject. For some respondents, the uncertainty was confirmed in dialogue with the data collector.
7. Conclusions and perspectives

The conclusions of this thesis will be presented in this chapter. The perspectives and implications for policy and practice as well as for future research will also be discussed and presented.

7.1 Conclusions

In this thesis, several aspects of the influence of generic substitutions on pharmacy practice have been analyzed. The research questions have been approached using both qualitative and quantitative study designs and the results contribute to a deeper understanding of how, why and how often patients, pharmacists and their communication in community pharmacies are affected.

In conclusion, the results of the four papers underlying this thesis indicate that although pharmacists consider generic substitution to have shifted the focus of communication with the patient from pharmaceutical counseling to cost and regulations, the actual pharmacist-patient communication contains little medical communication regardless of whether or not generic substitution is offered. During dispensing encounters where generic substitution is offered, more time is spent talking about non-medical issues. However, the encounter is not longer in total nor is more time spent talking about medical issues. The number of pharmaceuticals was the only one of the studied factors associated with more communication about medical issues, although the same non-significant tendency is seen for patients with a higher level of education.

Prior experience with changes in effect and side effects were associated with low trust in interchangeable medicines, as was the opinion that generic substitution complicated the respondents’ medicine use. One in three medicine users considers their use of medicine more complicated after generic substitution, and as many report less effect or more side effects, in line with pharmacists’ concerns about patients’ ability to handle generic substitution due to increased complexity. Patients’ trust in the interchangeable medicines eligible for generic substitution was also found negatively associated with lower level of education and female gender. Beliefs about personal and societal financial gain from generics substitution and information from the physician were associated with high trust.
Comparison with other studies shows that the results obtained were often in line with previous findings. The results provide new information about how generic substitution can influence different aspects of pharmacy practice in Swedish community pharmacies. However, it is not known to what extent they can be translated into other countries.

7.2. Perspectives and implications
A pharmaceutical policy such as generic substitution, implemented with the sole aim of lowering the price of pharmaceuticals, also has consequences that reach beyond competition on the pharmaceutical market. The results reported in this thesis indicate that in contrast to what is described in the literature, the role of the pharmacist is becoming more administrative. This trend is most likely not due to generic substitution alone. However, in order for generic substitution to reach its goal of lowering the cost of medicines without comprising healthcare objectives, the government as well as pharmacy owners and community pharmacists must focus on assuring that patients receive the support and information they need. Moreover, although generic substitution is conducted by the pharmacist, it is implemented and handled by the patient. Any changes to the policy should therefore always consider the implications for the patient, whether direct in the form of new product names or appearance, or indirect, such as an increased administrative focus by the pharmacy.

7.2.1. Perspective and implications for practice and policy
Based on the results of the studies underlying this thesis, the following policy and practice measures for policymakers, authorities and professionals concerned with the development and improvement of the current system for generic substitution are suggested:

1. *Strengthen the ability and motivation of healthcare professionals to communicate with and inform the patient regarding generic substitution and overall medicine use.*

Measures could be educational interventions as part of basic education or continuing education at the local pharmacy (chain). Moreover, should communication training be included in the pharmacy education program to reflect that the scope of pharmacy practice today includes patient-centered care.
2. Adjust the surveillance and compensation model for pharmacies to promote quality counseling.

A stronger effect on the quality of counseling is seen when defined in regulatory requirements. Based on current regulations, the government wants pharmacies to do their part to optimize health in the population. However, today’s counseling surveillance does not signal the importance of focusing on quality counseling, nor does the model for compensation to pharmacies, based only on the number of medicine packages sold. An alternative model to encourage development where the competence at community pharmacies is better used in line with current regulations could include penalties for lack of counseling or additional reimbursement for good counseling services.

3. Always assess the patient’s ability to comprehend and handle substitution.

Since healthcare professionals are in contact with each patient during prescribing and dispensing, difficulties with substitution should be identified early, addressed and followed up, both at the doctor’s office and at the community pharmacy. For instance, measures could be a “no” to substitution or providing additional time to talk about the patient’s medicine use in relation to generic substitution.

4. Consider saying “no” to substitution for patients who perceive a difference in effect or side effects.

Less effect or more side effects after a substitution, whether experienced or measured, compromise the outcome of treatment and hence need to be addressed. For this group of patients, “no” to generic substitution could be an option that should be used more often. The effects of such a measure on the efficacy of the generic substitution model should, however, be carefully monitored.

5. Make stricter regulations regarding similarities in appearance and packaging.

The fourth study underlying this thesis confirmed previous findings regarding patient confusion over changes in appearance and name of pharmaceuticals. This problem could be addressed by sharpening the regulations regarding interchangeability, so that they include similarities in appearance and packaging.
6. **Introduce generic prescribing**

Generic prescribing or international non-proprietary name (INN)-prescribing is indicative or obligatory in 23 out of 27 EU countries(7). Generic prescribing means that instead of choosing an interchangeable generic, the doctor prescribes the active substance that will be on the prescription. Generic prescribing increases focus on the active substance, which is always the same, and hence lessens the confusion with regard to changes in product names(153). However the INN or generic name can be more complex than the product name, and thus has been claimed to be more difficult for patients to remember, which does not improve patient safety. For this reform to be effective, it would moreover need to be combined with strict regulations regarding name and packaging.

7.2.2. **Perspectives for future research**

The impact of cost containment policies on quality of care is often unclear(12). Quality in regard to healthcare can be determined by the success of improving patients’ health status at the lowest cost(154). Although a large number of studies from different parts of the world have investigated different aspects of generic substitution, relatively little attention has been paid to how the quality of care including pharmacy practice is influenced. Financial constraints from the government or other actors have always been hard to balance with healthcare objectives. Moreover, since many pharmacies are privately owned and run like a business, different agendas enter into practice, including constraints on sales and time. The results in this thesis indicate that little or no medical communication takes place during dispensing, irrespective of generic substitution, which confirms studies in other countries. This finding should be investigated further, especially in relation to the incentives for pharmacy owners and pharmacists, to prioritize high quality counseling.

Moreover, based on the fourth study in this thesis the trust in the bioequivalence seems to be lower among Swedish patients compared to Danish and Finish. No one have however conducted a Nordic comparative study of how generic substitution has influenced professional practice as well as patients in the different Nordic countries. While there are differences in how generic substitution is regulated and performed this would provide important information about the effect of regulatory differences in regards to outcome and patient safety.
8. References


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LIST OF APPENDICES

The layout of the paper and reference list corresponds to the style required or preferred by the respective journals.


Status: *Submitted*.

**Appendix 4**: Olsson, E., Wallach Kildemoes, H., Carlsson, E., Hällkvist, C., Kaae, S., Kälvemark Sporrong, S. The case of generic substitution: What factors influence the patients’ trust in bioequivalence?

Status: *Manuscript*.
Appendix 1

Olsson, E., Kälvemark Sporrong, S. Pharmacists’ experiences and attitudes regarding generic drugs and generic substitution: two sides of the coin.

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Pharmacists’ experiences and attitudes regarding generic drugs and generic substitution: two sides of the coin

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Keywords
experience; generic drug substitution; pharmacists; pharmacy practice; Sweden

Abstract

Objective  Generic drug substitution reduces costs for medicines, but the downsides include unintentional double medication, confusion and anxiety among patients. Information from pharmacists affects patients’ experiences of substitution with generic drugs. The aim of this study was to explore experiences and attitudes to generic substitution among Swedish community pharmacists.

Methods  An interview guide was developed. Semi-structured interviews with community pharmacists were conducted and transcribed verbatim. Analysis was inductive; extracts from the transcripts were compared and combined to form themes and subcategories. Pharmacists from a heterogeneous convenience sample of pharmacies were interviewed until data saturation had been achieved.

Key findings  Sixteen pharmacists were interviewed. Three main themes and twelve subcategories were identified, with the main themes being the role of the pharmacist, pharmacists’ concerns regarding patients, and the generic drug. Pharmacists found it positive that generic substitution decreases the costs for pharmaceuticals but also emphasized that the switch can confuse and worry patients, which could result in less benefit from treatment. Respondents claimed that generic substitution has changed the focus in the pharmacist–patient meeting towards economics and regulations.

Conclusion  According to the interviewed pharmacists generic substitution is not primarily an issue of generic versus brand-name products, but concerns above all the challenges that the switch implies for patients and pharmacists. To prevent known confusion and concerns among patients it is important that community pharmacists acquire the necessary tools and knowledge to manage this situation; pharmacists themselves as well as pharmacy owners and authorities share responsibility for this.

Introduction

Substitution of brand-name drugs with generic drugs is common practice worldwide to reduce escalating costs for medicines. However, healthcare professionals and patients have questioned whether the cost savings are eroded by increasing total medical costs as the substitution may result in increased non-adherence and other drug-related problems. This would not only deprive the patient of the benefits of treatment but also possibly lead to serious adverse events. The effects of generic substitution on adherence have been studied but outcomes are non-conclusive, showing poorer as well as improved adherence associated with the use of generics.

Studies on patients’ opinions about generic substitution have shown that a majority of patients are positive about the switch. However, side effects, therapy failure, anxiety and confusion have been associated with substitution. The fear of side effects and uncertainties about the similarity of the brand-name and generic medicines are some reasons for patients’ worries. The change in product name, package appearance and package size is confusing and challenging to many patients.

Studies have found both positive and negative attitudes towards generic substitution among pharmacists. The pharmacists’ perceptions are, among other factors, influenced by their experiences with patients.

Patient generic drug use and whether or not they approve of substitution is affected by pharmacists’ and physicians’
attitudes and recommendations. Pharmacists are the healthcare professionals who meet the patient when the actual switch takes place, so they obviously play an important role in generic drug use. Information about generics has been shown to strongly affect whether or not the patient accepts substitution. It has also been shown that patients who receive longer sessions of pharmaceutical counselling report increased feelings of safety.

In Sweden generic substitution was introduced in October 2002. It then became mandatory for dispensing pharmacists to offer the cheapest available generic equivalent pharmaceutical that is included in the pharmaceutical benefit scheme. The patient can, however, choose not to substitute the prescribed drug but will then have to pay the price difference between the cheapest available generic and the prescribed drug. At the time that generic substitution was introduced, and up until the end of 2009, all Swedish pharmacies were state-owned; no pharmacists owned their own pharmacy nor had any economic interest in pharmacy profits. Also, prices as well as margins for pharmacies in Sweden were (and still are) decided by a governmental authority. The introduction of generic substitution did reduce the increase in costs of pharmaceuticals for patients as well as for the government.

The aim of this study was to explore Swedish community pharmacists’ attitudes and experiences regarding generic drugs and generic substitution. Attitude is in this context defined as ‘a settled way of thinking or feeling about something’.

Methods

Pharmacies were asked to participate in the study, chosen with consideration to size, pharmacy profile, surrounding environment and geographic dispersion, striving for heterogeneity in the sample. The pharmacies were located in two larger and two smaller municipalities, in two different regions of Sweden. Pharmacists in the selected pharmacies were invited to be interviewed. Availability of pharmacists, due to workload and work schedule, were determining factors for how many pharmacists were interviewed at each workplace. In recruiting respondents the focus was on achieving heterogeneity with respect to age, working experience, sex and education among the interviewees. Pharmacies and interviewees were recruited until saturation was considered to have been achieved; that is, when interviews no longer added any new information. Face-to-face semi-structured interviews were performed individually by the first author (EO, in October 2009) at the respondent’s workplace. An interview guide containing open-ended questions was developed, guided by findings from previous research. A pilot interview was held using the first draft of the interview guide. No questions were removed or added as a result of the interview. Themes covered in the interview guide were: attitudes about generic drugs and generic substitution, knowledge, education and potential measures. Examples of questions were: What do you think about generic substitution? What is your opinion on generic drugs? According to you, what are the advantages/disadvantages with generic substitution? and What kind of training or information have you received about generic substitution? Probing was used to expand on responses. Interviews were digitally recorded and transcribed verbatim before analysis.

Ethical approval was not considered necessary by the regional ethical review board of Uppsala. Ethical considerations were met, however; informed consent was requested from participants and interviewees cannot be identified.

The transcripts were read repeatedly and relevant words/phrases were extracted, then compared and combined to form categories. The categories were derived inductively; that is, obtained gradually from the data. Categories were pulled together into main themes. The categorization process was initiated by both authors coding three interviews together. The initial categorization was done primarily by the first author and, when completed, audited by and discussed with the second author, who has a different disciplinary background within social sciences. As both researchers became more familiar with the data, categories were continually modified and specified. After the initial categorization, some subcategories were rearranged, renamed, merged if they overlapped, or divided if they contained different types of data to ensure that categories were exhaustive and consistent but distinct from each other. There were few disagreements about the analysis; those that arose were thoroughly looked at and discussed until consensus was reached.

The results are illustrated by quotes from the interviews. Each pharmacist was given a number, which is given after each quotation.

Results

In total six pharmacies were asked to participate, and one declined due to heavy workload. Respondents were continually recruited until saturation was considered to be achieved which was after 16 interviews with pharmacists from five pharmacies. Each interview lasted approximately 30 min (range 12–36 min). One to five pharmacists were interviewed at each pharmacy. A majority of the respondents were female and ages varied from 25 to 64 years; the extent of pharmacy working experience also varied (see Table 1). Most respondents had several years of experience working with generic substitution.

All respondents seemed to have a nuanced attitude to mandatory generic substitution, being both positive and negative, by acknowledging the pros and cons of generic substitution. The results showed that the reform seemed to have affected pharmacists and their daily work in a variety of ways. Analysis
of the data resulted in three main themes and a total of twelve subcategories, presented in Table 2. Subcategories are italicized in the following text.

The role of the pharmacist in generic substitution

The importance of pharmacist–patient communication and of building trust was highlighted by the interviewees. The pharmacists emphasized the importance of making the patient feel safe and to motivate him/her to take the substituted drug. Respondents considered it important to maintain a neutral opinion; even so, some felt as though they directed the patient towards switching by stating that this is the same drug at a lower cost.

A main concern among the interviewed pharmacists was that subjects such as money, finances, equivalence, generic drugs, package, excipients and colouring had started to dominate patient–pharmacist communication since the introduction of generic substitution.

. . . we want to talk about how the medication affects you as a customer. . . . That’s what we want to talk about, [but] we talk a lot about money and generic substitution and excipients and colouring agents, and all kinds of things that we don’t really want to talk about. (Ph16)

Instead the respondents wanted the conversation to focus on the treatment, advice about the medications, preventive actions, strengthening and clarifying the prescriber’s aims and making sure that the patient realises the importance of adherence.

The interviewees had experiences of patients only wanting the drug their physician had prescribed. This did not necessarily have to be the original brand.

If they [the physicians] prescribe one specific manufacturer the patient wants the one prescribed. . . . Then it doesn’t matter if I tell them that it is the same active substance. (Ph3)

Many respondents argued that it would be optimal if the prescriber informed the patient that the drug might have a different name when being dispensed at the pharmacy. Patients who are aware of the generic substitution when entering the pharmacy are, according to the pharmacists, more likely to approve of the switch and appear to feel less insecure. Respondents also argued that if the patient’s physician does not consider the generic equally efficient it is hard for the patient to do so.

According to the respondents, the introduction of generic substitution had consequences for the pharmacists as it had resulted in more (non-fruitful) discussions with patients as well as other time-consuming extra work; for example, more complicated storage. Many pharmacists said they found it demanding, aggravating and tiring to discuss the substitution.

I think it is tiresome sometimes to try to explain to customers, it turns into time-consuming discussions and that happens daily. (Ph3)

Some, however, found the discussions positive as they were able to use their pharmaceutical knowledge more when trying to make the patient understand the substitution.

Some pharmacists were concerned about exposing patients to potential risks, especially referring to patients who are hypersensitive to excipients.

When talking about the patients’ perception of the pharmacists most respondents stated that patients appeared to trust the pharmacist. One respondent, however, expressed concern about pharmacists losing credibility when stating that it is exactly the same drug, as a patient can come back very upset and blame the pharmacist if he/she experienced less effect or side effects from the substitute drug.

A vast majority of the respondents claimed not to have received any information or education, neither provided at their workplace nor during their pharmaceutical education, on generic substitution, generic drugs or on how to handle patient communication regarding the switch, at least not that they remembered.

### Table 1 Characteristics of the pharmacists interviewed

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>48 years (25–64 years)</td>
</tr>
<tr>
<td>Pharmacy working experience, median (range)</td>
<td>21 years (0.5–47 years)</td>
</tr>
</tbody>
</table>

### Table 2 Themes and categories

<table>
<thead>
<tr>
<th>Main theme</th>
<th>Subcategories</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The role of the pharmacist in generic substitution</td>
<td>Pharmacist–patient communication, The physicians’ role, Patients’ perceptions of the pharmacist, Information and education</td>
</tr>
<tr>
<td>2. Pharmacists’ concerns regarding patients</td>
<td>Confusion and compliance, Patient reactions, Potential measures</td>
</tr>
<tr>
<td>3. The generic drug</td>
<td>The financial aspect, The pharmacists on equivalence, Patients’ perceptions about generic drugs, The generic industry</td>
</tr>
</tbody>
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Pharmacists’ concerns regarding patients

Most interviewees expressed concerns about patients not understanding the substitution. They were afraid that the switch confuses patients, who thereby more easily mix up their pharmaceuticals, possibly resulting in disruption of treatment or double medication.

The potential loss of compliance and thereby possible lack of effect following generic substitution can, according to the respondents, also result in higher doses than necessary being prescribed. Most of the respondents recalled having discovered double prescription, double administration, disruption in drug use and patients who not dare to take the ‘new drug’.

It happens quite often that customers don’t think their ‘new drug’ works as efficiently [as the old one] or that they report on having side-effects. (Ph9)

They especially pointed out elderly as a vulnerable group with a high degree of polypharmacy, resulting in an extensive amount of drugs in different shapes, colours and names for the patient to keep track of.

They have a special memory of how they look. There should be seven white ones. And then come some red ones, that must be wrong. . . . So maybe they take seven white ones, but there happen to be two of the same kind. (Ph16)

Patients using antipsychotics were also considered extra sensitive as they, according to the pharmacists, more often react negatively towards the switch. Respondents argued that the lowered costs might be at the expense of patients’ health and quality of life.

According to the respondents most patients do not question or comment on the substitution nor do patients react negatively to the switch but consider it to be positive as they are offered a cheaper alternative. Some patients, however, get upset and question whether it is the same drug. Several pharmacists stated that substitution can be highly demanding for patients who do not feel well when using the substitute drug, or are afraid of an allergic reaction or side effects. Respondents stated that if the patient does not believe in the drug being equally effective he/she is more likely to experience side effects or no effect from the treatment.

Some respondents pointed out potential measures to optimize the mandatory substitution and also the patients’ experience with the switch. Generic prescription was requested, as was more information from the physician to the patient about the substitution, as well as improved communication and increased cooperation between the physician and the pharmacist. The importance of making the prescribers more aware of the generic substitution was also mentioned.

Many respondents also expressed that it would be optimal if the tablets and package of the generic drug looked more like the reference drug. It was also suggested that the name of the active ingredient should be in bigger print than the invented name or name of the manufacturer.

To prevent confusion among the elderly one pharmacist suggested that patients over a certain age not be included in the mandatory generic substitution. An upper limit was also suggested concerning the number of generic drugs for each brand-name drug.

A couple of respondents claimed that the patients need more information, both from pharmacists and physicians, to improve the use of generics. They also requested increased input from pharmacists regarding the design and planning of these kinds of systems before introducing them.

The generic drug

The financial aspect with increased price competition on the pharmaceutical market and the decrease in cost of pharmaceuticals, both for society and patients, were considered to be positive.

You save a lot of money, so I think it’s positive. That’s money that can be better used in the healthcare system. (Ph2)

Respondents claimed that the lower prices enable treatment for patients with limited economy, and saves money for the society.

At the same time, several of the respondents questioned whether society actually does save money in the end as the cost savings may be eroded by increasing total medical costs due to lower adherence and worried and confused patients.

I fear that what the healthcare system is saving on one hand, they have to spend on the other, because the patients aren’t aware that they’re taking the same medicine. In the worst case they’re taking two or three at the same time. (Ph1)

The majority of the interviewed pharmacists considered generic drugs equivalent to and as effective as their reference medicinal product. Respondents stated that they trust the
manufacturers and that the decision from the authorities is correct.

\[\ldots\text{you have to trust that}\ldots\text{they have done all the evaluations and studies, so what I can do is just to present the final results for the customer, here we have two interchangeable [medications]. (Ph7)}\]

Several, however, expressed some doubt and questioned the reliability of generic drugs after having met many patients who claim to experience great differences.

Some stated that they agreed with patients regarding generic drugs sometimes not being as ‘classy’ as the brand-name drug referring to, for example, a lack of coating and poorer blister labelling.

According to the pharmacists some patients’ perceptions about generic drugs are that they are of lower quality because they are cheaper. Furthermore, the change in colour, shape, name and package appearance of the pharmaceutical results in the resistance towards the switch among the patients. Pharmacists reported that patients often argue that the generic drug is not equivalent to the drug they had prior to the switch, referring to a lack of effect or new side effects. These reports are, according to the respondents, seldom passed on to authorities due to inadequate information and/or lack of time. One pharmacist further claimed that some patients base their perceptions of the generic drug on where the product has been manufactured, not trusting generic drugs that have been produced in low-income countries.

Some pharmacists thought that the introduction of generic drugs on the market and the subsequent expansion of the generic industry could constitute a risk for future medical research and the development of new drugs.

**Discussion**

It is obvious that political reforms with one aim, in this case to save money, also have other consequences. This study demonstrates that there are two sides of the coin: pharmacists find it positive that generic substitution saves money, but also highlight that the switch means extra work, and can confuse and worry patients, which could result in less benefit from treatment.

This study has added important knowledge about the pharmacists’ perspective on a pharmaceutical health reform and how it affects their day-to-day work life. It also has some limitations. Even though heterogeneity was strived for, few men were interviewed. Very few men work in Swedish pharmacies and very few men worked at the pharmacies that participated in the study. It cannot be ruled out that men have different views, and that saturation was not reached in this aspect. The respondents could have been influenced by the fact that the interviews occurred at their workplaces. On the other hand, they were in environments familiar to them and the interviews were conducted in isolation.

The first author is a pharmacist, which could affect her analysis of results. She had, however, never worked with dispensing of prescribed drugs at the time of the interviews and analysis. Data were also analysed by the second author, who is not a pharmacist but has a different disciplinary background, which added another perspective to the analysis and hopefully counterbalanced the risk of bias.

Pharmacists working in Swedish community pharmacies emphasize the financial aspect of mandatory generic substitution, considering the lowered costs for both patients and society to be the most important benefit. This was the reason behind the reform, and is an obvious gain for society at large as well as individual patients. However, as discussions and counselling regarding generic substitution focus more on finances and health policies, pharmacists’ expertise is not taken advantage of, and pharmaceutical counseling is possibly omitted. In itself this could lead to negative health outcomes for the patients, and also to moral distress among pharmacists as they feel unable to retain their professional interests and values. The substitution also places additional time constraints on pharmacists and there is an increased need for professional judgement, which, for example, increases the risk of medical errors. It is important that community pharmacists’ get tools and knowledge to manage this situation; pharmacists themselves as well as pharmacy owners and authorities share responsibility for this. The interviewed pharmacists were concerned about patients becoming confused and worried when receiving a generic instead of the prescribed drug. Generic prescribing was requested to prevent confusion, as was implementation of standards for similarity between generics and reference drug referring to tablet and package appearance. Another major concern is the name change. Changes in the labelling of packages, so that the name of the active ingredient is shown in larger type than the invented name or name of the manufacturer, were suggested to prevent mix-ups and misunderstandings. These are practical changes that obviously would make the substitution less challenging for patients.

The respective roles and responsibilities of physicians and pharmacists in generic substitution seem unclear. Collaboration is desirable, not least to make patients secure about their drug use, and to avoid reduced compliance as previous studies have shown might follow generic substitution. Good communication and information needs to follow the patient with the prescription, from the prescribers desk do the pharmacy counter. Some respondents were not convinced that the generics and the reference drugs are equivalent, confirming earlier findings. As pharmacists’ and physicians’ attitudes are important for patients’ acceptance of the generic drug this could have an impact on patient compliance and hence on patient health.
Most respondents in this study claimed not to have received any information or education on generic substitution or on related patient communication and more education on this was requested. A short introduction to the reform was nevertheless supposed to have taken place as background material (mostly on how to handle the technical parts of substitution) was distributed by the government pharmacy company’s head office to each pharmacy. It was, however, up to each manager to decide to which extent this was actually put forward (L. Lisper, Apoteket AB, personal communication). It has been shown earlier that many pharmacists do not correctly define generic medicines, confirming the need for education. With large-scale reforms such as this, professionals, who are to carry out political decisions, need education and support in order to fulfill the requirements in a professional way. This goes for pharmacists as well as prescribers. As it has been shown that more positive responses in all domains of communication and beliefs about generics are associated with better generic drug use, measures ought to be taken to empower Swedish pharmacists in counselling regarding generic medicines, for instance by communication training.

This study demonstrates that new healthcare reforms focusing on costs need sufficient implementation and follow-up strategies in order to work well in healthcare practice.

Many actors, including the government, authorities, universities, employers, professional organizations and individuals, have responsibilities when it comes to minimizing the possible negative consequences of generic substitution, and thus maximizing the obvious benefits.

Conclusions
According to the Swedish pharmacists interviewed, generic substitution brings about challenges for patients as well as for pharmacists. To prevent confusion and concerns among patients pharmacists need to know how to communicate information about the substitution effectively in order to promote and ensure correct drug use. Not until known problems and difficulties are addressed can the obvious advantage of generic drugs – that is, cost savings, making more and/or other therapies possible – be fully enjoyed.

Declarations
Conflict of interest
The Authors declare that they have no conflicts of interest to disclose.

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Acknowledgements
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References


Appendix 2


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Original Research

Pharmacist–patient communication in Swedish community pharmacies

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Abstract

Background: It is important that pharmacists counsel patients about their prescribed medicines, as it leads to improved therapeutic outcome, increases compliance, and decreases confusion and insecurity. Studies have shown that the number of patients getting any pharmaceutical counseling varies greatly. Swedish pharmacists claim that the focus of the dialog with the patient has switched from pharmaceutical counseling to economy and regulations.

Objective: The aim of this study was to determine the content and time disposition of the patient–pharmacist communication during dispensing of prescribed medicines at Swedish community pharmacies.

Method: Non-participant observations and audio recordings were used as data-collecting methods. The content of the dialog was categorized into 2 deductively decided main categories–medicinal and non-medicinal issues–and 12 inductively decided subcategories.

Results: A total of 282 pharmacy encounters were observed and recorded, of which 259 fully coincided with the inclusion criteria. After categorizing the content of each encounter the results showed that there was little or no dialog regarding medicinal issues during the pharmacy encounter in Swedish community pharmacies. Forty percent of the dialog concerns non-medical issues and almost half of the encounter was silent.

Conclusion: Medicines are an essential treatment method in healthcare, and pharmaceutical expertise is available to patients who enter a community pharmacy. The results of this study show that today's pharmacy encounter is not focused on improving the use of medication, possibly resulting in the patient not gaining the most benefit from his or her treatment.

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Key words: Communication; Community pharmacists; Community pharmacy; Sweden

Background

Communication between pharmacist and patient is of great importance for achieving desired patient satisfaction as well as for improving appropriate medication use and treatment outcome.1–5

Pharmacists’ counseling of patients about their prescription medications has been shown to result in higher rates of patient compliance and to improve therapeutic outcomes.6,7 Other key benefits such as improved patient understanding and reduction
in patient anxiety as well as increased pharmacist status, satisfaction and self-esteem have been found as a result of pharmacists’ good communication skills.\(^8,9\)

Efficient, motivating, and purposive communication is one of the most important tools in the patient meeting and hence in pharmaceutical counseling.\(^10\) Different patients have different expectations regarding the pharmacy encounter,\(^11\) but a precondition for a meaningful medicine dialog at the pharmacy counter is that the patient wants to be a part of a healthcare provider-patient alliance. Reasons for patients to turn down an invitation for dialog include finding the dialogue irrelevant, failing to understand the reason for questions asked, or lack of agreement to the pharmacist’s taking control (sometimes seen as unwelcome) of the customer’s medication.\(^12\) Patient–pharmacist interactions have been seen to be significantly longer if pharmacists use a participatory approach with patients.\(^13\) The degree of interaction with patients has been found to be affected by how busy the pharmacy is, the age of the pharmacist, therapeutic class, and state regulations.\(^14,15\) Reported counseling rates, i.e., the proportions of patients receiving counseling, have however been found to vary from 8% to 100%.\(^16\)

According to the International Pharmaceutical Federation (Fédération Internationale Pharmaceutique (FIP)) and the World Health Organization (WHO), pharmacists should “provide advice to ensure that the patient receives and understands sufficient written and oral information to derive maximum benefit from the treatment.”\(^17\) In Sweden, community pharmacists are obligated to give the patient personalized information, and they also must ensure that he or she knows how to use the medicines.\(^18\) Pharmacists should also make sure that the patient is achieving the desired effects from the drugs prescribed.\(^19\) An observation study conducted in Swedish community pharmacies concluded that most patients took on a passive role, asking on average 3 questions per encounter of which one-third were related to medicine.\(^20\) Furthermore, Swedish pharmacists state that new health policies such as the introduction of mandatory generic substitution have resulted in an unwanted change of the content and focus of the dialogue from health and medical information toward finances and politics.\(^21\)

Pharmacists have the potential to contribute to an improved use of medications. Communication is an essential tool in this process.\(^9\) There is, however, a lack of studies regarding the content of the communication in pharmacies, and also about whether more time is being spent on “non-medical” matters than on medicinal consultation. Knowledge about the communication in community pharmacies could be valuable to develop pharmacy encounters—and consequently to improve adherence and enhance therapeutic outcomes.\(^9,10\)

**Objective**

The aim of this study was to determine the content and time disposition of the patient–pharmacist communication during dispensing of prescribed medicines at Swedish community pharmacies. Exploration was particularly done of how much time is spent on medical versus non-medical matters.

**Method**

Data were collected with non-participant observations and audio recordings of the communication between pharmacists and patients during prescription dispensing at community pharmacies.

**Study sample**

Community pharmacies were selected with the aim of achieving a heterogenous sample in regard to geographic location, pharmacy ownership, size, surrounding environment, and socioeconomic factors. Six community pharmacies, in total, were initially asked to participate. One declined and was replaced by another pharmacy with similar profile. All pharmacists working at each pharmacy were invited to participate. The observers consecutively approached patients who were waiting to be attended to.

Ethical approval was not considered necessary by the regional ethical review board of Uppsala. Ethical considerations were however met; informed consent was requested from the patients and pharmacists before observation began. The participation was voluntary and data confidentiality was ensured.

**Data collection**

Twenty-three observations were used to pilot the data-collecting strategy. A procedure for the observation and the observation protocol was developed based on the experiences from the pilot. The observation protocol was used to register if something happened during the
dispensing that could not be registered audibly, for instance if a third person was waiting aside the patient. The first author, who conducted the pilot observations, then instructed the other 2 observers on their first day at each pharmacy.

The 3 first authors conducted observations during the fall and early winter of 2011. The data collection took place on different days of the week including weekends, and at different times during the day, to include as wide a variety of patients as possible. Only patients who were picking up prescription medications for themselves were included in the study.

If the patient chose to participate, the observer awaited the patient’s turn to be attended to, and then followed the patient to the counter, where an audio recorder was placed. The observer then left the counter so that the conversation could take place in private. The encounter was followed visually by the observer to cover events that might not be noticed or were unclear in the recording, such as if a third person was present. This was documented in the observation protocol.

Data analysis

All verbal communication between the pharmacist and the patient, as well as silences longer than 3 s, were coded for occurrence and time duration. All 3 observers participated in the analysis to better capture the complexity in the data and circumvent the biases of any one person. Before initiating analysis approximately, one-third of all audio-recorded observations were transcribed verbatim.

Two main categories, Medical subjects and Non-medical subjects, were previously decided according to study aim, while subcategories were inductively arrived at. After listening to and reading through the transcribed observations, preliminary subcategories were identified. Ambiguities in classifications and uncertainties regarding definitions of the categories were discussed as the coding procedure proceeded, a total of 6 meetings, until consensus was reached. Previously coded observations were re-coded to match any changes in category definitions during the coding procedure. Fifteen observations, 2 or 3 from each pharmacy, were coded by all 3 coders and inter-rater reliability was calculated, using Cohen’s kappa. The Cohen’s kappa value for rater A and B was calculated to be 0.90, for rater B and C 0.89, and for rater A and C 0.87, which indicates a very good strength of agreement between the coders.

Results

Study population

Out of 32 invited pharmacists working at the 6 participating pharmacies, 29 (90.6%) volunteered to participate, of which 27 were female. In total, 407 patients were approached and 282 agreed to participate, giving a participation rate of 69.3%. Few stated reasons for turning down the invitation but those who did most often referred to lack of time. Observations with poor sound quality, affecting the ability to hear the conversation were excluded. Observations that were not fully recorded, for instance if the pharmacist and the patient moved away from the counter out into the pharmacy to look at over-the-counter medicine, were also excluded. Observations that did not comply with the inclusion criteria, for instance observations with more than 1 patient interacting in the encounter, were excluded as well. For the analysis 259 observations remained (91.8% of participating patients). 174 (67.2%) of these were female.

Patient–pharmacist communication

In addition to the 2 predefined main categories, 12 subcategories were identified.

Little time, 11 (median) or 25 (mean) s, was spent talking about medical or pharmaceutical issues, i.e., issues that the pharmacist is educated to deal with. Half of the observed dialogs spent
10 s or less on medical/pharmaceutical issues (see Table 2), and in 22.4% of dialogs there was no communication on these issues at all.

The largest subcategory within the medical main category was user instructions. These include the question “Have you had this medicine before?”, which was asked by the pharmacist in 44% of the observations. This question was coded as “user instructions” as the information normally given when a patient answered “no” was user instructions. The question was thus considered a way to decide whether to give user instructions or not. Other issues in this subcategory mostly concerned when and how to take the medicine and how to store it.

More time was spent on non-medical than on medical subjects. The most time in this main category was spent on communication about the prescription as such or administration related to the prescription. This category mainly included discussions on whether the prescription was available in the pharmacy computer software, was valid or too old, which of several prescribed medicines the customer wanted to collect, as well as customers asking for summaries of prescribed medicines. The second largest subcategory, other non-medical issues, included greetings, talk about the weather or similar subjects, and directing the customer to other parts of the pharmacy.

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean (s)</th>
<th>Median (s)</th>
<th>SD (s)</th>
<th>Min–max (s)</th>
<th>95% confidence interval (for mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Medical/pharmaceutical information</td>
<td>4.20</td>
<td>0</td>
<td>11.22</td>
<td>0–78</td>
<td>2.83–5.57</td>
</tr>
<tr>
<td>1b. Adverse effects, risks, etc.</td>
<td>4.25</td>
<td>0</td>
<td>13.61</td>
<td>0–118</td>
<td>2.59–5.92</td>
</tr>
<tr>
<td>1c. User instructions</td>
<td>12.08</td>
<td>5.00</td>
<td>17.67</td>
<td>0–121</td>
<td>9.92–14.24</td>
</tr>
<tr>
<td>1d. Other medical/pharmaceutical content</td>
<td>4.52</td>
<td>0</td>
<td>12.37</td>
<td>0–80</td>
<td>3.01–6.03</td>
</tr>
<tr>
<td><strong>Total: Medical/pharmaceutical</strong></td>
<td><strong>24.84</strong></td>
<td><strong>11.00</strong></td>
<td><strong>40.82</strong></td>
<td><strong>0–283</strong></td>
<td><strong>19.85–29.84</strong></td>
</tr>
<tr>
<td>2a. The prescription, technical</td>
<td>40.44</td>
<td>31.00</td>
<td>35.86</td>
<td>4–257</td>
<td>36.06–44.83</td>
</tr>
<tr>
<td>2b. Computer problems</td>
<td>0.61</td>
<td>0</td>
<td>3.82</td>
<td>0–39</td>
<td>0.14–1.08</td>
</tr>
<tr>
<td>2c. Reimbursement</td>
<td>4.12</td>
<td>0</td>
<td>9.65</td>
<td>0–52</td>
<td>2.94–5.30</td>
</tr>
<tr>
<td>2d. Generic substitution, technical</td>
<td>9.80</td>
<td>0</td>
<td>22.68</td>
<td>0–188</td>
<td>7.03–12.58</td>
</tr>
<tr>
<td>2e. Additional sales</td>
<td>3.39</td>
<td>0</td>
<td>11.24</td>
<td>0–101</td>
<td>2.01–4.76</td>
</tr>
<tr>
<td>2f. Payment</td>
<td>7.76</td>
<td>5.00</td>
<td>8.39</td>
<td>0–53</td>
<td>6.74–8.79</td>
</tr>
<tr>
<td>2g. Availability</td>
<td>6.39</td>
<td>0</td>
<td>20.38</td>
<td>0–183</td>
<td>3.89–8.88</td>
</tr>
<tr>
<td>2h. Other non-medical content</td>
<td>12.28</td>
<td>7.00</td>
<td>14.47</td>
<td>0–83</td>
<td>10.51–14.05</td>
</tr>
<tr>
<td><strong>Total non-medical</strong></td>
<td><strong>84.69</strong></td>
<td><strong>72.00</strong></td>
<td><strong>64.03</strong></td>
<td><strong>10–493</strong></td>
<td><strong>76.85–95.52</strong></td>
</tr>
<tr>
<td>Silence</td>
<td>111.57</td>
<td>88.00</td>
<td>88.95</td>
<td>0–495</td>
<td>100.69–122.46</td>
</tr>
<tr>
<td><strong>Total time</strong></td>
<td><strong>225.76</strong></td>
<td><strong>183.00</strong></td>
<td><strong>151.95</strong></td>
<td><strong>35–1288</strong></td>
<td><strong>207.17–244.36</strong></td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 s or less</td>
<td>49.8</td>
</tr>
<tr>
<td>11–30 s</td>
<td>24.7</td>
</tr>
<tr>
<td>31–60 s</td>
<td>15.8</td>
</tr>
<tr>
<td>61–90 s</td>
<td>3.9</td>
</tr>
<tr>
<td>91 s or more</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Discussion

This study aimed to determine the content and time disposition of the patient–pharmacist communication during dispensing of prescribed medicines at Swedish community pharmacies. It was observed that little or no time was spent on oral communication related to medical subjects, i.e., little or no pharmaceutical information was given by pharmacists or asked for by patients. Communication related to non-medical subjects such as practical administrative information about the prescription, information about generic substitution, the pharmaceutical benefit scheme and payment was, however, found to engage 40% of the total time of the encounter.

Medicines are an essential treatment method in modern healthcare, and pharmaceutical expertise is available to every patient that enters a community pharmacy in Sweden. This expertise seems, however, to be underused from the perspective of
patients and society. As pharmacist counseling can enhance compliance as well as improve therapeutic outcomes, the lack of communication related to medicinal subjects reported here possibly means that important information is omitted and that Swedish medicine users do not get as much value from the pharmacist encounter as they could.

Why, then, is the communication not focused on medical and pharmaceutical issues? Swedish community pharmacists are according to legislation obligated to give personalized information and assure that the patient knows how to use his or her medicines. The results from this study indicate that they do not do so. The amount of counseling has earlier been found to correlate with pressure from legislation. How authorities check on whether these requirements are met in the pharmacy encounter is, however, unclear. While other aspects of pharmacies such as storage and availability of medicines as well as appropriateness of the premises are thoroughly controlled by authorities in Sweden, the pharmaceutical information in the pharmacist-patient dialogue is not. If the government wants pharmacists to contribute to optimizing the health of the population (which they do, considering the legislation), then a follow-up in terms of checking is also essential in this area.

Another explanation could be the lack of incentive for pharmacy owners to focus their attention and business on quality of pharmaceutical counseling. It has been shown that remuneration is a facilitator for implementation of cognitive services within pharmacy. In Sweden, the profit lies in increased selling of medicines or other merchandise, and not in providing pharmaceutical counseling. This is a result of the construction of the Swedish system, where the actual sale of medication is remunerated. The cognitive factor—using the pharmacists’ knowledge and skill to optimize drug use—is not. A focus on customer satisfaction rather than medication use and patient safety can put the patient at risk. By indirectly letting the patients decide whether or not they have time for or need pharmaceutical information and counseling, pharmacists might omit important information, miss out on side effects, on interactions, or on inappropriate use of medicine.

Patients also have different expectations and demands when entering a pharmacy; some only want to purchase their medicine as quickly as possible while others want information and/or consultation about their medication. The patient is, in many cases, not aware of whether he or she is using the medicine incorrectly. Patients lacking earlier experience of good quality pharmacist counseling might also be unaware of the expertise of the pharmacist, i.e., of what help and support they can actually get at the pharmacy counter.

The pharmacists’ behavior is obviously crucial to the outcome of the encounter. Regulations, as well as ethical guidelines, emphasize their roles as caregivers, i.e., using their expertise to enhance medication use and hence its outcome. Patients need knowledge and support in order to be able and motivated to undergo medicine therapy. Pharmacists ought to know this, and also feel that they have a responsibility as healthcare professionals. The results of this study indicate that this is not the case. Or are administrative systems (e.g., handling the prescription as such) and other regulations (e.g., reimbursement systems) counterproductive in the patient–carer relationship? Should other employees take care of more administrative issues in order to make the pharmacist’s role clearer?

Good communication skills among pharmacists are seen to have many positive effects on health outcome as well as on patient satisfaction. They are also a necessary tool in the dialogue with the patient to identify problems with his or her drug use, effects of the treatment, interactions, side effects and so on. The questions the pharmacist asks are of great importance for the patient’s compliance and the therapeutic outcome. Today there are no communication courses in the university pharmacist education programs in Sweden. The communication training that pharmacy students do get is mainly during their internship. Note, however, that this “training” occurs when the patient is right in front of them. Without communication training during the pharmacist education the new graduates, even though they possess adequate pharmaceutical expertise and knowledge, will be unable to embrace the challenge of patient consultation.

Politicians, pharmacy owners, universities, authorities, and pharmacists need to take responsibility for demanding as well as creating a pharmacy environment where providing high quality pharmaceutical counseling is routine practice.

The results from this study show that pharmaceutical expertise seems to be under-used. Today’s pharmacy encounter is not focused on improving the use of medication, possibly resulting in the
patient not gaining the most benefit from his or her treatment.

**Limitations**

One advantage of observational methods is that they study what people actually do, not what they say they do.26 However, the methods also have limitations. A major problem is the observer effect, i.e., that people who are aware of being observed (as in this study) may change their behavior.27

The change of behavior is generally thought to be for the better—observed persons might want to show their best behavior. In this study the observed pharmacists knew that the observers came from the university. It can hence be hypothesized that they, if they changed their behavior, did this in a way that enhanced pharmaceutical counseling (i.e., in the real world there is even less pharmaceutical counseling). Or they could have been afraid to give “wrong advice” and hence avoid pharmaceutical content in their dialogs. The patients may also have refrained from posing questions due to the observation. Most patients, who gave a reason for not participating in the study, said that it was because of lack of time. This could potentially result in the counseling sessions in the study on average being longer than in reality since those patients possibly want the dispensing to be as quick as possible, and hence have shorter encounters.

One way to overcome the observation effect is to observe for longer periods of time, so that persons observed get accustomed to the situation.27 In this case each observer spent about a week in each pharmacy, and this might to some extent have made pharmacists familiar with the situation.

**Conclusion**

This observational study of 282 encounters between pharmacists and patients in Swedish community pharmacies found, after categorizing the content of each encounter, that little or no time was spent on dialogue regarding medicinal issues. Forty percent of the dialogue concerned non-medical issues and almost half of the encounter was silent. Medicines are an essential treatment method in healthcare, and pharmaceutical expertise is available to patients who enter a community pharmacy. The results of this study show that today’s pharmacy encounter is not focused on improving the use of medication, possibly resulting in the patient not gaining the most benefit from his or her treatment. Politicians, pharmacy owners, universities, authorities, and pharmacists need to take responsibility for demanding as well as creating a pharmacy environment where providing high quality pharmaceutical counseling is routine practice.

**Acknowledgments**

We would like to thank the pharmacy owners, pharmacy managers, dispensing pharmacists and patients that participated in this study.

**References**


Status: Submitted.
The influence of generic substitution on the content of patient-pharmacist communication in Swedish community pharmacies

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Abstract

Introduction
Prescribed medicines must be used correctly in order to provide an optimal outcome. Individual counseling about medicines is a core activity in community pharmacies, and found to improve adherence. Generic substitution has been claimed, but not confirmed, to deter focus from pharmaceutical counseling in community pharmacies. The objective was to study the relationship between the extent and content of patient-pharmacist communication in community pharmacies and generic substitution in relation to other variables earlier found relevant for communication: number of prescriptions, and socio-demographic factors.

Material and Method
The study was conducted in 6 community pharmacies in Sweden. Non-participant observations with audio-recordings were made and short structured interviews conducted. Out of 32 pharmacists 29 agreed to participate (90.6%), as did 282 out of 407 patients (69.3%). Full recordings and interviews were obtained from 231 encounters. Logistic regression analysis was applied to calculate odds ratio for occurrence of generic substitution. Linear regression (β-coefficients) was applied to test predictors for time spent on different categories.

Results
More time was spent on non-medical issues (β, 0.32, p=0.01) in encounters were generic substitution occurred. However, the total time of the encounter was not longer when controlled for number of prescriptions (β, 0.21, p=0.38), nor was more time spent on medical issues (β, -0.13, p=0.22). The amount of time spent on non-medical issues increased with age.
of patient (age 41-60: β, 0.55, p<0.001). The results further indicate that more time was spent on medical issues with patients who have a higher education (high school: β, 0.18, p=0.07, university: β, 0.17, p=0.11).

Conclusion
Occurrence of generic substitution is correlated with more time spent on communicating on non-medical issues. However, time spent on medical issues is not longer, despite pharmacists considering generic substitution to complicate patients’ use of medicines. No extra time was spent on medical information for the groups of patients normally overrepresented among those with low health literacy. This study suggests that pharmacists are more reactive than proactive when counseling patients on medicines and needs to further embrace their role in promoting rational use of medicines and assuring patient safety, not least when generic substitution occurs.

Keywords: Generic substitution, community pharmacy, communication, Sweden
Introduction

For a treatment regime to have an optimal outcome, it is usually essential for prescribed medicines to be used as recommended by the health care professionals. Incorrect use of medicines can result in great suffering for patients and potentially lead to death. Pharmacists are the healthcare professionals most readily accessible to the public. In addition to dispensing medicines, they provide patients with information and individualized advice about medicines and how to use them, the core activities of community pharmacies. Pharmaceutical counseling in community pharmacies has been shown to improve adherence, result in better treatment outcomes e.g. better glycemic control in people with type II diabetes, make patients feel safer about their medications and enhance patient empowerment.

The WHO and the International Pharmaceutical Federation as well as many national authorities state that pharmacists should provide advice about the medicine and its use when dispensing. However, the proportion of pharmacy encounters that actually involve medical counseling have been found to vary from 8-100%. Studies in Sweden have shown that 18-22% of dispensing encounters at community pharmacies contain no medical dialogue.

Factors influencing the occurrence and/or extent of a medical dialogue include the pharmacist’s age, time of day and/or busyness of the pharmacy, patient’s age and gender, the therapeutic class of medicine the patient is receiving, whether it is a first or repeat prescription, and counseling regulations. A Swedish study identified another possible factor, as pharmacists claimed that generic substitution (GS) influences communication with the patient, as they had experienced that it switches the focus from medical issues to cost and regulations, possibly resulting in the omission of important counseling. To our knowledge, it has not been confirmed that GS influences communication in this way.

Aim of study
The objective was to study the relationship between the extent and content of patient-pharmacist communication in community pharmacies and generic substitution in relation to
other variables earlier found relevant for communication: number of prescriptions, and socio-demographic factors.

**Ethical approval**
Although the regional ethical review board of Uppsala did not consider ethical approval necessary, the board issued an official advisory statement. Informed consent from patients and pharmacists was asked for prior to observation and interviews, participation was voluntary and data confidentiality ensured.

**Material and methods**

Data was collected through non-participant observations\(^\text{18}\) and short structured interviews with patients at 6 Swedish community pharmacies selected from different counties to give a heterogeneous sample as described earlier.\(^\text{12}\) Of the 32 pharmacists working at the 6 pharmacies on the days data was collected, 29 volunteered to participate, resulting in a 90.6% pharmacist participation rate.

Inclusion criteria for patients were: 18 years of age or more and visiting the pharmacy to collect at least one prescription for self. A total of 282 out of 407 patients agreed to participate, giving a participation rate of 69.3%. The most frequently stated reason for not participating was lack of time.

Patient-pharmacist communication during dispensing of prescribed medicines was audio-recorded and the encounter visually observed (notes taken) from a distance. The interviews, mainly containing questions regarding socio-demographic factors (gender, education level, age, country of birth), were conducted with patients before or after dispensing.

**Data analysis**
The content of the patient-pharmacist communication was categorized into 2 predetermined main categories: communication about medical issues such as user instructions, side effects, indication; and communication about non-medical issues such as cost, regulations e.g. reimbursement systems, administrative issues. Total time and the time for each category in each dialogue was measured (dialogue including both pharmacist and patient). Silence longer than three seconds was also registered. The categorization has been described in
Bi- and multivariable analyses were used to explore factors associated to the different categories of time spending. Multivariable analyses were used to explore the impact of GS on patient-pharmacist communication, while taking into account other relevant variables likely to influence communication, such as socio-demographic variables or number of prescriptions being collected.

Six explanatory variables were included in the analysis: age, gender (patient), education level, country of birth, number of prescriptions the patient wanted to collect (number of prescriptions) and occurrence of GS, see table 1.

The number of prescriptions the patient wanted to collect was determined on the basis of the information in the patient-pharmacist communication in the audio-recordings, and was categorized in 0-6+ products due to few observations with more than 6 prescriptions. Occurrence of GS was defined as when a generic substitution was possible, i.e. when the patient was offered a GS, independent of whether the patient accepted or rejected the substitution, or when a pharmacist substituted the patient’s pharmaceutical without informing the patient of the possibility to accept or reject. Occurrence of GS was identified from the audio-recordings and based on the information in the patient-pharmacist communication.

Some encounters were excluded due to non-fulfillment of the inclusion criteria (n=9), poor sound quality (n=2), incomplete recording of the full encounter (n=12), and incomplete interviews (n=28) resulting in 231 participants. The characteristics of the involved pharmacy customers were summarized by calculating the distribution (%) of the different categories in each of the explanatory variables, see table 2.

**Bivariable analyses**

The bivariable association between time spent in the encounter and the explanatory variables (occurrence of GS, number of products and socio-demographic characteristics) was assessed for the 3 different time categories: total time, medical time, non-medical time. For each level
of the explanatory variables, the following 3 measures for time spent were calculated: median value (50% percentile), and a range corresponding to the 90th and 10th percentiles.

Spearman’s Rho was calculated for the linear relationship between number of prescriptions (1-6+) and each of the three time measures.

**Multivariable analyses**

Due to few observations in the youngest age group, the four age categories were merged into three for the multivariate analyses. Furthermore, one record missing information on education was excluded, as well as observations without information on number of prescriptions patients wanted to collect (n=20) or with no valid prescriptions (n=4), resulting in 206 observation for the multivariable analyses.

Logistic regression analysis was applied to calculate odds ratio (OR) for occurrence of GS according to number of products (continuous variable) and socio-demographic characteristics (dummy variables), applying 95% confidence intervals (CI).

Linear regression was applied to calculate β-coefficients for different types of time spent in the encounter (continuous outcome variable, in minutes), applying number of products (continuous variable) as primary explanatory variable and socio-demographic characteristics (dummy variables) as dummy co-variables. T-tests and robust standard errors were applied to test the null-hypothesis of no linear correlation, applying 95% CI.

**Results**

Of the patient participants, 44.2% were aged 60+, the majority were women (67.5%), and born in Sweden (90.1%). GS occurred in less than one-third of the encounters, and more than half of participants wished to collect only one pharmaceutical product, whereas 3.4% wished to collect more than 5 products, and no information was available for 8.7% (20), see table 2.

INSERT TABLE 2 AROUND HERE
Table 3 shows the bivariate association between the time spent on each category for all socio-demographic characteristics, occurrence of GS and number of prescriptions. The median total time spent increased with age and number of prescriptions, but decreased with length of education. Occurrence of GS was associated with longer total time spent and more non-medical time spent compared to no occurrence of GS (244 vs 167 seconds). The same trend was seen for number of prescriptions. The association between number of prescriptions and more medical time was less clear. More medical time spent when GS occurred was only found within the 90th percentile. The total time of an encounter ranged from 34 to 1206 seconds, time spent on medicinal issues from 0 to 283 seconds and non-medical issues from 10 to 493 seconds (silence 0-494 seconds).

**Table 3**

Table 4 shows the results of the logistic regression analysis, exploring odds ratio (OR) for occurrence of GS including number of prescriptions patients wished to collect as well as socio-demographic variables. Odds for GS to occur increased significantly with the number of prescriptions the patient wanted to collect (OR=1.81, p<0.001, 95% CI 1.38-2.48). Older people tended to have higher odds for occurrence of GS than younger people at same levels of other variables, but with insignificant estimates (p>0.05 and large confidence intervals). This was also the case for participants born outside Sweden (p>0.05 and large confidence intervals). Spearman’s Rho showed a linear correlation between number of prescriptions and the three time categories (data not shown).

**Table 4**

Table 5 shows the results of the linear regression analysis of increases in different types of encounter time (in minutes) as function of number of products (1-6+) adjusted for occurrence of GS and socio-economic variables (dummy variables). Time spent increased significantly (p<=0.05) with number of products (N) for all categories of time spent, but most markedly for total time (1.29 minutes/N). There was no other significant association regarding total time spent, although men seemed to have shorter encounters (β=0.45, p=0.07).
Significantly more time was spent on non-medical issues in encounters where GS occurred compared to encounters without (β, 0.32, p=) i.e. 0.32*1.29 minutes/N. However, no significant difference was found in the time spent on medical issues (β, -0.13, p=0.22) or the total time of the encounter (β, 0.21, p=0.38). A significant correlation was also found between time spent on non-medical issues and patient age, with more time spent on non-medical issues with patients’ increasing age (patients 41-60: β, 0.23, p=0.08, patients 60+: β, 0.55, p<0.001). This correlation was not seen for time spent on medical issues or total time of encounter, see table 5.

Time spent on medical issues was only significantly correlated with number of prescriptions the patient wanted to collect. However, there was a non-significant tendency for a higher level of education to be associated with more medical counseling (high school: β, 0.18, p=0.07, university: β, 0.17, p=0.11).

Discussion

The results show that the occurrence of GS was significantly correlated with more time spent communicating about non-medical issues. However, the total time of the encounter was not longer when controlled for number of prescriptions the patient wished to collect, nor was more time spent on medical issues. The number of prescriptions that the patient wanted to collect was also found to positively correlate with the total time of the encounter, the amount of time spent on medical issues and the time spent on non-medical issues. The amount of time spent on non-medical issues increased with patients’ age. The result further indicates that more time is spent on medical issues with patients who have a higher education and that men have shorter consultations.

The primary strength of this study is that 1) the communication was captured with audio-recordings providing unbiased material, and 2) that qualitative and quantitative analysis was combined to achieve a more complete understanding of factors co-varying with the patient-pharmacist communication. Some limitations to this study should be noted. First, both patients and pharmacists knew that they were being observed and the communication audio-
recorded. However, all participants received information regarding the anonymity of their participation, and the observations were non-participant and made from a distance. Observers placed in the middle of the activities are known to be more intrusive than those who stand to the side. 19 Also, in an attempt to reduce observer effects, the observers collected data at each pharmacy for a longer duration (one week), which familiarized pharmacy staff with the situation. 18 Secondly, the pharmacies were not selected randomly, meaning that the results cannot be generalized to all dispensing encounters in Swedish community pharmacies. As the study aimed to yield insight about patient-pharmacist communication under different conditions of practice, the sample instead aimed at heterogeneity. Thirdly, it cannot be excluded that non-respondents differed from the persons who accepted participation, as no non-response analysis was made.

More time is spent on non-medical issues for encounters where GS occurred compared to encounters without, confirming earlier indications, i.e. that pharmacists claim to spend more time on non-medical dialogue when GS occurred. 17 This indicates that discussions relate to e.g. prices rather than in-depth explanations on e.g. how the switched medicines relate to each other. However, the total time of the encounter was not longer when controlled for number of prescriptions the patient wished to collect, nor was more time spent on medical issues.

Studies have found that GS worries and confuses some patients, 20-22 possibly resulting in double medication or reduced adherence. 23,24 Moreover, some Swedish pharmacists worry about patient safety as they consider GS to make it more challenging for the patients to keep track of their medicines. 17 Patients’ negative attitudes towards GS have been shown to correlate with receiving less information on the subject. 22 Hence, this study provides an explanation for why many patients are still worried about GS, as it shows that pharmacists have not yet managed to integrate more medical counseling into encounters containing GS.

The results also indicate that pharmacists spend more time on medical issues with patients who have finished high school or university compared to patients with a lower level of education. With older patients, although pharmacists spend more time talking about non-medical issues, they do not spend more time on medical issues. The concept of health literacy is often used to describe patients’ ability to gain access to, understand and use health information. 25 Individuals with low health literacy are more likely to be men, over the age of 60, and have less than a high school education. 26 In the current study, 2 of these factors are
correlated with a shorter encounter (men), and less medical dialogue (lower level of education). Neither factor is associated with a longer medical dialogue, although from a health literacy perspective, it is important for this group to get additional support.\textsuperscript{27} It has been shown that patients with limited health literacy skills ask fewer questions\textsuperscript{28,29}; although they may want and need information clarified and may hide lack of understanding out of embarrassment or shame.\textsuperscript{27}

This study suggests that the content of patient-pharmacist communication in Swedish community pharmacies is reactive rather than proactive; dependent on which questions the patient asks rather than what information the patient might need. Hence it is important for pharmacists to be able to identify groups that need more medical information and dialogue, including groups with low health literacy and when GS occurs. Pharmacists should embrace this responsibility.

**Conclusions**

This study shows that occurrence of GS is significantly correlated with pharmacists spending more time communicating with patients about non-medical issues. However, when controlled for the number of prescriptions, the total time of the encounter is not longer, nor is more time spent on medical issues, despite pharmacists considering that GS complicates patients’ use of medicines. Further, no more time was spent on medical information for the groups of patients normally overrepresented among individuals with low health literacy.

While pharmacists recognize the potential challenge generic substitution introduces, this study indicate that they need to embrace the importance of their role in promoting rational use of medicines and assuring patient safety by providing additional support. Moreover, community pharmacists should be more aware of that groups of patients with low health literacy, especially in the case of GS, might be in need of additional support and hence spend more time on medical counselling.
Role of funding and conflict of interest
This study was partly funded by the Actavis Scholarship for Pharmacy Practice Research awarded by Actavis AB in collaboration with the Swedish Academy of Pharmaceutical Sciences. The study was planned and conducted with no interference from any of the funders.

Conflicts of interest: none.

Acknowledgements
The authors would like to thank the pharmacy owners, pharmacy managers, dispensing pharmacists and patients that participated in this study. We also would like to thank Douglas Lundin for early discussions on statistics.
References


**Table 1. Overview of outcome and explanatory variables.**

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>Explanatory variables</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time of encounter</td>
<td>Occurrence of generic substitution*</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Time spent on medical issues</td>
<td>Number of prescriptions</td>
<td>0, 1, 2, 3, 4, 5, 6+</td>
</tr>
<tr>
<td>Time spent on non-medical issues</td>
<td>Socio-demographic variables</td>
<td></td>
</tr>
<tr>
<td>Occurrence of generic substitution*</td>
<td>• Age</td>
<td>&lt;20, 21-40, 41-60, 60+</td>
</tr>
<tr>
<td></td>
<td>• Country of birth</td>
<td>Sweden, Other</td>
</tr>
<tr>
<td></td>
<td>• Education level (highest level</td>
<td>Elementary School,</td>
</tr>
<tr>
<td></td>
<td>finished )</td>
<td>High School, University</td>
</tr>
<tr>
<td></td>
<td>• Gender</td>
<td>Male, Female</td>
</tr>
</tbody>
</table>

*Applied as outcome in logistic regression analyses and as explanatory variable in bivariable and linear regression analyses*
Table 2. Study population/encounter characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occurrence of generic substitution</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69.3 (160)</td>
</tr>
<tr>
<td>Yes</td>
<td>30.7 (71)</td>
</tr>
<tr>
<td><strong>Number of prescriptions (mean 1.62)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.7 (4)</td>
</tr>
<tr>
<td>1</td>
<td>57.1 (132)</td>
</tr>
<tr>
<td>2</td>
<td>18.6 (43)</td>
</tr>
<tr>
<td>3</td>
<td>7.4 (17)</td>
</tr>
<tr>
<td>4</td>
<td>3.0 (7)</td>
</tr>
<tr>
<td>5</td>
<td>1.7 (4)</td>
</tr>
<tr>
<td>6+</td>
<td>1.7 (4)</td>
</tr>
<tr>
<td>Missing</td>
<td>8.7 (20)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>3.5 (8)</td>
</tr>
<tr>
<td>21-40</td>
<td>21.2 (49)</td>
</tr>
<tr>
<td>41-60</td>
<td>31.2 (72)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>44.2 (102)</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>93.1 (215)</td>
</tr>
<tr>
<td>Other</td>
<td>6.9 (16)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0.4 (1)</td>
</tr>
<tr>
<td>Elementary School</td>
<td>15.2 (35)</td>
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<tr>
<td>High School</td>
<td>34.8 (92)</td>
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<td>University</td>
<td>44.6 (103)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67.5 (156)</td>
</tr>
<tr>
<td>Male</td>
<td>32.5 (75)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100 (231)</td>
</tr>
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</table>
Table 3. Time disposition for the patient-pharmacist communication: median, 10th (p10) and 90th (p90) percentile of each category (total time of dispensing encounter, time spent on medical information, time spent on non-medical information) for all variables.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total time (seconds)</th>
<th>Non-medical time (seconds)</th>
<th>Medical time (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>p10</td>
<td>p90</td>
</tr>
<tr>
<td>Occurrence of generic substitution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>167</td>
<td>80</td>
<td>356</td>
</tr>
<tr>
<td>Yes</td>
<td>244</td>
<td>126</td>
<td>505</td>
</tr>
<tr>
<td>Number of prescriptions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>59</td>
<td>34</td>
<td>227</td>
</tr>
<tr>
<td>1</td>
<td>139</td>
<td>82</td>
<td>283</td>
</tr>
<tr>
<td>2</td>
<td>214</td>
<td>155</td>
<td>359</td>
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<tr>
<td>3</td>
<td>225</td>
<td>142</td>
<td>508</td>
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<tr>
<td>4</td>
<td>382</td>
<td>244</td>
<td>556</td>
</tr>
<tr>
<td>5</td>
<td>405</td>
<td>299</td>
<td>463</td>
</tr>
<tr>
<td>6+</td>
<td>565</td>
<td>476</td>
<td>1206</td>
</tr>
<tr>
<td>Missing</td>
<td>296</td>
<td>107</td>
<td>559</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>114</td>
<td>86</td>
<td>212</td>
</tr>
<tr>
<td>21-40</td>
<td>142</td>
<td>67</td>
<td>376</td>
</tr>
<tr>
<td>41-60</td>
<td>192</td>
<td>97</td>
<td>364</td>
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<tr>
<td>&gt;60</td>
<td>204</td>
<td>108</td>
<td>474</td>
</tr>
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<td>Country of birth</td>
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<tr>
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<td>179</td>
<td>88</td>
<td>439</td>
</tr>
<tr>
<td>Other</td>
<td>228</td>
<td>99</td>
<td>338</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>370</td>
<td>370</td>
<td>370</td>
</tr>
<tr>
<td>Elementary School</td>
<td>227</td>
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<td>High School</td>
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<td>University</td>
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<td>86</td>
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</tr>
<tr>
<td>Male</td>
<td>174</td>
<td>93</td>
<td>378</td>
</tr>
<tr>
<td>Total</td>
<td>173 5</td>
<td>97</td>
<td>383</td>
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</table>
Table 4. Odds ratio (OR) for occurrence of generic substitution.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of prescriptions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1.81 (1.34-2.43)</td>
<td><strong>0.00</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 (ref)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>41-59</td>
<td>1.73 (0.71-4.25)</td>
<td>0.23</td>
</tr>
<tr>
<td>60+</td>
<td>1.78 (0.73-4.36)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
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<td></td>
</tr>
<tr>
<td>Sweden (ref)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.13 (0.70-6.42)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary School (ref)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>0.99 (0.36-2.75)</td>
<td>0.99</td>
</tr>
<tr>
<td>University</td>
<td>0.93 (0.34-2.54)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
</tr>
<tr>
<td>Female (ref)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.65 (0.31-1.33)</td>
<td>0.24</td>
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</table>
Table 5. Linear correlation coefficient (β) for number of prescriptions, generic substitution, age, education, gender and country of birth as predictors of differences in patient-pharmacist communication (total time of dispensing encounter, time spent on medical information, time spent on non-medical information).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total time (minutes)</th>
<th>Non-medical time (minutes)</th>
<th>Medical time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>(95% CI)</td>
<td>β</td>
</tr>
<tr>
<td>Occurrence of generic substitution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.00</td>
<td>(0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>Yes</td>
<td>0.21 p=0.38</td>
<td>(-0.26-0.69)</td>
<td>0.32 p=0.01</td>
</tr>
<tr>
<td>Number of prescriptions (1-6)</td>
<td>1.29 p&lt;0.001</td>
<td>(0.87-1.70)</td>
<td>0.41 p&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>0.00</td>
<td>(0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>41-60</td>
<td>0.11 p=0.76</td>
<td>(-0.58-0.79)</td>
<td>0.23 p=0.08</td>
</tr>
<tr>
<td>&gt;60</td>
<td>0.30 p=0.35</td>
<td>(-0.33-0.94)</td>
<td>0.55 p&lt;0.001</td>
</tr>
<tr>
<td>Country of birth</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>0.00</td>
<td>(0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>Other</td>
<td>0.29 p=0.51</td>
<td>(-0.57-1.15)</td>
<td>-0.09 p=0.64</td>
</tr>
<tr>
<td>Education</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Elementary School</td>
<td>0.00</td>
<td>(0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>High School</td>
<td>-0.15 p=0.64</td>
<td>(-0.80-0.49)</td>
<td>-0.14 p=0.44</td>
</tr>
<tr>
<td>University</td>
<td>-0.21 p=0.59</td>
<td>(-0.97-0.55)</td>
<td>-0.22 p=0.25</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.00</td>
<td>(0.00-0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>Male</td>
<td>-0.45 p=0.07</td>
<td>(-0.93-0.03)</td>
<td>-0.12 p=0.33</td>
</tr>
</tbody>
</table>
Appendix 4

Olsson, E., Wallach Kildemoes, H., Carlsson, E., Hällkvist, C., Kaae, S., Kälvemark Sporrong, S.
The case of generic substitution: What factors influence the patients’ trust in bioequivalence?

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Patients’ trust in the bioequivalence of substitutable generics. What factors are important?

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\textbf{Abstract}

Generic substitution is a cost-containment strategy meant to contain pharmaceutical expenditure without compromising health objectives. In effect generic substitution offers patients the bioequivalent generic with the lowest price instead of the prescribed product. Patients’ perceptions of and trust in the bioequivalence of exchangeable products (generics and brand medicines) can be crucial for adherence, received effect and side effects. The purpose of this survey was to assess how prior experiences, information from pharmacist or doctor, difficulties with adherence after generic substitution, view on financial savings, acceptance of generic substitution and socio-demographic factors are associated with Swedish patients’ of trust in the bioequivalence of interchangeable medicines. Questionnaires were handed out at 12 community pharmacies in the north, middle and southern parts of Sweden. A total of 719 patients participated (response rate 85.7%). The results show that a majority (70.7%) of the respondents trust the bioequivalence. Of the studied variables, experiencing more or less effect after generic substitution, experiencing more or fewer side effects, saying no to the substitution, having a lower level of education and female gender, as well as holding the opinion that changes in product name and appearance make adherence more complicated were seen to significantly increase the odds of low trust in bioequivalence. Trust in societal and personal savings from generic substitution and information from the doctor significantly decreased the odds on low trust. This study provides new knowledge for decision makers and professionals concerned with the development and improvement of the current system for generic substitution, and can hopefully contribute to achieving a system that is optimal for the individual patient as well as society.

\textbf{Introduction}

Generic substitution means that patients are offered the cheapest substitutable pharmaceutical instead of the prescribed product at the community pharmacy. This pharmaceutical policy and cost-containment strategy is implemented in a wide range of countries and the number of off-patent medicines entering the market is increasing\cite{1}. Generic substitution was introduced in Sweden in 2002 and has been shown effective, lowering the cost of pharmaceuticals for patients and the government by billions (SEK) every year and resulting in some of the lowest prices on
off-patent medicines in all of Europe [2]. However, studies have found that GS confuses and worries patients, possibly resulting in mix ups, double medication and non-adherence thereby posing a risk to patient safety [3-7]. Patients also report reduced effect of treatment or new side effects from GS [3, 4, 8, 9].

Nordic studies have reported that the majority of patients are positive about GS [3, 5, 10, 11], and that patients who accepted a generic switch did not have more concerns about their medicine than patients who did not switch [12]. However, studies show that about one-third of the patients reported negative experiences such as side effects or poorer effect from GS [3, 8, 13, 14], partly due to medication errors [14]. It has also been found that 29% of patients were anxious when they started using a generically substituted product, their main worries being fear of side effects and uncertainties about the similarity of the drugs [4].

Level of education, gender, prior experience with GS and income have been shown to influence patients’ acceptance [8, 15-18]. Recommendations, information and the perceptions of physicians and pharmacists have also been found important to patients’ experience and acceptance [3, 10, 19, 20]. Anxiety reduction has been shown to be especially effective when the advice of the physician is in direct line with that of the pharmacist [3]. Patients’ perceptions of the received product and trust in the bioequivalence of exchangeable products (generics and brand medicines) can be crucial for adherence, received effect and side effects [21-23].

A high substitution rate is a desirable goal for policymakers as well as taxpayers to encourage competition on the pharmaceutical market and lower the cost of medicines. However, it is only a desirable goal if patients trust the medicine they purchase from the pharmacy. Trust in equality has been proven important to receive the full benefit of a treatment, also in the case of GS [23]. Hence, it is relevant to study what factors are correlated with low trust in the bioequivalence between interchangeable medicines. By assessing which of previously identified factors are relevant for Swedish patients’ trust, this study can provide a broader knowledge base for decision makers and professionals concerned with the development and improvement of the current system for generic substitution. Hopefully this will contribute to more effective interventions and changes in regulations leading to generic substitution that is more optimal for the individual patient as well as society. The aim of his study is hence to assess how prior experiences, information from pharmacist or doctor, difficulties with adherence after GS, view on financial savings, acceptance of GS and socio-demographic factors are associated with patients’ low level of trust in the bioequivalence of interchangeable medicines.

Method and material

Study setting
The Swedish healthcare system is tax funded, and the degree of reimbursement for pharmaceuticals increases with patients’ expenses for prescription medicines included in the pharmaceutical benefits scheme [24]. The patient pays a maximum of 2200 SEK within a period of 12 months for pharmaceuticals included in the pharmaceutical benefits scheme. All costs in excess are subsidized by the government until the end of the 12-month period.
Mandatory GS was first implemented in Sweden 2002. Based on clinical data from the manufacturing pharmaceutical company, The Swedish Medical Product Agency decides which pharmaceuticals with the same amount of active substance and same formula are to be considered bioequivalent and thereby exchangeable [25, 26]. All Swedish pharmacies must provide patients with the cheapest interchangeable product which once a month is appointed by the Dental and Pharmaceutical Benefits Agency and referred to as “the preferred product of the month”. The prescriber or the pharmacist can oppose the substitution, for instance, on medical grounds. The patient can also choose the prescribed product instead of the bioequivalent one with the lowest price, but will then have to pay the price difference out of pocket.

**Study design**
This is a cross-sectional study with data collected at one point in time through a quantitative questionnaire handed out to pharmacy customers who have previously or currently use prescribed medicines and have had experience with GS.

**Questionnaire development**
A questionnaire was developed on the basis of previously identified factors relevant to patients’ trust in and acceptance of generic substitution [8, 15, 16, 18, 27]. The questionnaire included questions regarding socio-demographics and 13 items divided into three sections. Section 1 consisted of the views on generic medicine scale with four items developed by Rathe et al.[28], and questions regarding acceptance of GS. The response to the four items resulted in an index value from 1 to 5, which measured patients’ trust in the safety, quality and effect of cheaper interchangeable medicines. In this paper, the scale was reversed so that a high score equals a high level of trust (max =5) and a low score a low level of trust (min=1), in the interests of simplifying understanding of the results. Section 2 consisted of eight items concerning information regarding GS from physicians and pharmacists, as well as patients’ prior experiences with GS. Section 3 included five items regarding the financial aspect of GS and difficulties with changes in color/name. All items were answered on a 5-point Likert response scale. Two different scales were used: “Strongly agree, agree, don’t agree or disagree” and “always, often, sometimes (half of the time), seldom, never”. The questions regarding socio-demography included: age, gender, education level, native language, income, number of medicines taken daily and types of medicine.

The questionnaire was initially tested for content validity by two senior researchers with wide experience in quantitative and qualitative method design, and one researcher with vast knowledge in the field. Subsequently, 20 cognitive interviews with concurrent and retrospective “thinking aloud” and probing were carried out with medicine users focusing on comprehensibility, appearance and relevance[29]. Some changes were made to the questionnaire after the pilot to clarify questions and response scales. All pilot respondents were shown the new version of the questionnaire and approved the changes. Last, the feasibility of the data collecting procedure and comprehensibility of the final questionnaire was piloted at two different community pharmacies. A total of 41 questionnaires were handed out over two days to pharmacy customers who met
inclusion criteria. Minor modifications were made to the layout and order of questions post pilot.

**Sample selection**
The questionnaire was handed out at 12 pharmacies in 12 different municipalities. All 290 municipalities in Sweden were divided into 10 strata based on average yearly income (per household), which has been shown previously to influence patient preferences regarding generic substitution [27]. One municipality in each stratum was selected with the aim of representativity with regard to geography, size (number of inhabitants) and percentage of people born outside Sweden. In the two strata with more than 20% of the population, two municipalities were selected. One pharmacy was selected in each municipality with the aim of heterogeneity with regard to placement/surrounding and pharmacy owner (see table 1). Proportionate sampling was used to decide the number of questionnaires for each stratum, so that the number of questionnaires per strata would reflect to total number of individuals in each strata and hence the population[30].

**Data collection**
Pharmacy customers were approached consecutively inside or next to the entrance of the selected pharmacies. Those customers who had previously used prescribed medicines, been offered a generic substitution and spoke Swedish were invited to participate in the survey. The concept of generic substitution was clarified for all customers, and their informed consent requested before the questionnaire was handed out. Some customers (n=160) requested that data collectors read the questions to them, due to poor eyesight, for example. Gender and approximate age were registered for customers declining participation. Data were collected during March and April 2015. The days and times for data collection were varied to include all types of costumers. Data were collected during all opening hours on weekdays as well as over two weekends.

**Analysis**
For the analysis, the result from the scale “views on generics” was dichotomized (low trust≤3, and high trust>3) and applied as the outcome variable. The bivariable association between trust and the explanatory variables gender, age, education level, income, native language, number of pharmaceuticals per day, information received, prior experiences with changes in effect/side effects, confusion and financial aspects was assessed, see tables 1 and 2. The data for the items regarding prior experiences were dichotomized into groups of “have experienced” and “never experienced”. The two items regarding information from the physician and the two items regarding information from the pharmacies were merged into the items “information from the Doctor”, “information from the Pharmacist”. The responses were dichotomized into groups of “have received information” and “have never received information”. Moreover data were combined into two new items: “received information from both the pharmacist and the doctor” and “have never received any information”, and the responses dichotomized into “yes” and “no”. The response from the five items regarding confusion and financial aspects were dichotomized
with “strongly agree/agree” in one group and “neutral/disagree/strongly disagree” in another, see table 2.

The association between low trust and each of the explanatory variables (gender, age, education level, income, native language, number of pharmaceuticals daily, acceptance of generic substitution, prior experience with changes in effect/side effects, information received, confusion and financial aspects) was further assessed through crude odds ratios (OR) with 95% confidence intervals (CI) applying univariable (simple) logistic regression. Since almost all respondents (99.2%) had received information from pharmacists, this item was excluded.

Results

All pharmacy owners and pharmacy managers at the 12 pharmacies contacted regarding data collection at or near the pharmacy agreed to participate. A total of 849 pharmacy customers who met the inclusion criteria were invited to fill out the questionnaire; 719 agreed to participate, a response rate of 84.7%. Customers who declined participation most often gave lack of time as a reason, but some stated that they did not like questionnaires in general. Table 1 shows the population characteristics and average trust value. Data are displayed for each level of the studied variables and stratified into low trust≤3, and high trust>3 in the bioequivalence of interchangeable medicines. The majority of the participants were women (59.1%), the most common age group was 66-80 years old (44.5%), most common education level was university or equivalent (44.5%) and 93% had Swedish as their native language. Half of the study population was currently using three or more medicines per day, see table 1. Among the non-response group, 56% were women and 44% men. Based on estimated age, the no-respondents had an age distribution similar to the yes-respondents, with most non-responses in the group of 51-65 and 66-80 year-olds.

Patients trust in GS (range 1 to 5) was on average 3.75 (median) or 3.73 (mean), see table 1. The average trust value was lower among women than men. Moreover, trust decreased with increased age and number of pharmaceuticals. Patients with a lower education level and patients with lower income had a lower level of trust on average, see table 1. When stratified into groups of low and high trust, 70.7% of the respondents had high trust in the equivalence.

Table 2 shows the answers to the questionnaire items and the average trust in bioequivalence. The data are displayed for each level of the studied variables for all respondents and stratified by low and high trust. A majority (82.1%) of the respondents sometimes, often or always accepts generic substitution. The trust average among this group is 4 compared to 2.75 among those who seldom or never accept substitution. A majority (53.1%) of the patients with low trust in bioequivalence still accept substitution in most cases.
Almost one-third (29.6%) of the respondents had experienced less effect after substitution, and 22.1% more side effects. However, 18.4% had experienced better effect and 14.2% fewer side effects.

Almost all patients (99.2%) had received information about GS from a pharmacist at some point, while 65% had received information from a physician. Trust was slightly higher among patients who had received information from a physician (4.00) compared to those who had not (3.75). This was reflected in the stratified groups where a higher number of respondents had received information from the doctor (67.3%) compared to the low trust group (59.2%), see table 2.

Slightly more than one-third (36%) of the patients considered the change in appearance to complicate adherence. Changes in name was considered to complicate adherence by 40.8% of respondents. This was associated with number of medicines, where patients with a greater number of medicines were overrepresented in the group that found GS to complicate adherence. When asked if generic substitution saves money for society, 6.5% stated that they disagree or strongly disagree, while 68% agreed or agreed strongly. Regarding savings on a personal level, 13.2% disagreed or strongly disagreed with the statement "generic substitution saves money for me", while 66.4% agreed or strongly agreed. Most respondents (59%) were neutral with regard to the pharmacy making money on the substitution, see table 2.

Table 3 shows the result from the univariable (simple) logistic regression in the form of odds ratios (OR) for low trust with 95% confidence intervals (CI). The following groups were found to be significantly associated with increased odds of having low trust: female gender (OR: 1.96, 95% CI: 1.39-2.76), high school as highest finished level of education (OR: 1.72, 95% CI: 1.14-2.60), seldom or never accepting generic substitution (OR: 12.38, 95% CI: 7.89-19.43), previous experience with better effect (OR: 2.65, 95% CI: 1.78-3.96), less effect (OR: 11.30, 95% CI: 7.56-16.88), fewer side effects (OR: 4.37, 95% CI: 2.18-6.78), and more side effects (OR: 11.22, 95% CI: 7.42-16.96), of the opinion that changes in name (OR: 2.27, 95% CI: 1.63-3.15) or appearance (OR: 1.85, 95% CI: 1.33-2.58) are challenging, and of the opinion that the pharmacy profits from GS (OR: 2.08, 95% CI: 1.38-3.13). Having received information from the doctor (OR: 0.71, 95% CI: 0.51-0.98), or from both doctor and pharmacist (OR: 0.70, 95% CI: 0.50-0.97), strongly agree, agree or neutral to statement that GS saves money for me (OR: 0.28, 95% CI: 0.18-0.44) or for society (OR: 0.17, 95% CI: 0.09-0.32) were significantly associated with decreased odds of having low trust, see table 3.

Discussion
This study aimed to assess how prior experiences, information from pharmacist or doctor, difficulties with adherence after GS, view on financial savings, acceptance of GS and socio-
demographic factors are associated with patients’ low trust in the bioequivalence of interchangeable medicines. Overall the results show that a majority (70.7%) of the respondents trust bioequivalence. Out of the studied variables, experience with change in effect, experience with more or fewer side effects, lower level of education and female gender as well as opinions that changes in name and appearance make adherence more complicated were seen to significantly increase the odds of low trust in bioequivalence. Trust in societal and personal savings from GS and information from the doctor significantly decreased the odds on low trust.

The method used had two primary strengths. First, since questionnaires was handed out by a data collector according to a predetermined procedure, all respondents received the same information and were able to ask questions if any uncertainties arose with regard to questions [31]. Second, there was a high response rate (84.7%). This method also had some limitations. The labor-intensive method of having data collectors hand out the questionnaires kept the number of pharmacies where data were collected quite low which could have affected the representability. The gender distribution the study population was similar to the population medicine users in Sweden [32]. However, there was an underrepresentation of young medicine users and people in the lowest income level [32,33], and an overrepresentation of people with a university degree or equivalent [33]. While a low level of education was found to be associated with low trust levels, the level of trust found could be higher than the actual level among Swedish medicine users. The customers who declined to participate represented the study population as well as the population of medicine users with regard to gender distribution and estimated age. Finally, there were some questions that received low response rates or a high number of “neutral” answers, which could indicate that the question was hard to understand or did not feel relevant to respondents. A majority of the non-responses were due to the fact that the item in question was not applicable to the respondent, such as questions regarding change in effect for patients who had never agreed to substitution for a prescribed product. However, the item regarding profit for pharmacies received a large amount of neutral answers indicating uncertainty with regard to the question or no strong opinions on the subject.

The views on generic medicines scale has been used for Danish patients prior to this study. When applying the same dichotomization as Rathe et al, including index 3 (neither trust nor distrust) into the “high trust” group, 80% of the respondents in this study trusted in GS compared with 90.44% of Danish patients [28]. Results similar to those in Denmark were seen in Finland where 88.4% of patients held the opinion that cheaper generics are effective [11]. This result indicates that Swedish patients have a lower level of trust in the equivalence of cheaper generics then patients in Denmark and Finland. However, a majority of the patients with a low level of trust in the equality still accepted the substitution.

The results further show that about 30% have experienced less effect from their medication after a substitution, and almost every fourth patient more side effects, in line with previous studies reporting changes in effect and/or side effects after substitution [3, 4, 8, 9]. However, the results also show that about one in five has experienced better effect after the substitution and 14%
fewer side effects. Any change in effect or side effects, positive or negative, was seen to significantly correlate with low trust in bioequivalence. Although rigid requirements exist regarding the demonstration of bioequivalence in order to be eligible for GS [25, 26, 34], many patients still experience differences. With this study design, it is impossible to determine which came first: the patient’s low level of trust or experienced differences. While patients’ perceptions of received product and trust in the bioequivalence of generics and brand medicines have been found crucial for adherence, received effect and side effects [21-23], it is also likely that experiencing differences makes patients doubt equality.

It has previously been stated that patients are often unable to judge the efficacy of the medicine, but depend on others to assure a solid process of evaluation and approval of pharmaceuticals [35]. In Sweden, physicians have the option to refuse substitution for medical reasons: for instance, in cases where the patient has an allergy [36]. Difficulties being adherent after a substitution could also be a reason for saying no to GS. The results of this study show that more than one-third of patients considered that changes in appearance (36%) and name (40.8%) complicate their adherence. This factor was also significantly associated with lower trust in equivalence. While a doctor’s or pharmacist’s refusal to allow GS is an option, it can affect the cost of the prescribed medicine for the patient, as well as availability since the pharmacy might not have all generics in stock. Further, many refusals of substitution by doctors could not only result in a direct increase of costs to the patient, but could also affect prices generally due to a reduced market share for the preferred product of the month. The connection is that it would become less desirable for manufacturers of interchangeable medicines to compete on price to become the preferred product of the month [37]. The best choice for the individual patient and for society must therefore always be weighed in order to achieve a fair and cost-efficient healthcare system.

This study also shows that patients receiving information about GS from a doctor have greater trust in interchangeable medicines, which is in line with previous studies [3, 10, 19]. Moreover, patients with a lower level of education are more likely to have a low level of trust. This group of patients, together with men and the elderly, is found to be overrepresented in the group with low health literacy [38]. Health literacy is used to describe patients’ ability to gain access to, understand and use health information [39]. Additional support in the form of pharmacists spending more time on health information has been shown to be important for this group [40] as they often need more clarification, but are found to ask fewer questions [41, 42]. This finding suggests that while information is important, spending more time to assure understanding and trust in the efficacy of the interchangeable medicine is especially relevant for this group of patients.

Conclusion
The results of this study show that a majority of the respondents have a great degree of trust in the bioequivalence of generic medicines. However, the level of trust is lower than among patients
in neighbouring countries. More than one in three respondents consider the changes in name or appearance to complicate their adherence, and about one-third have experienced a change in effect and number of side effects after a substitution. This could compromise the outcome of the treatment and hence needs to be addressed. With limited resources available and a system that depends on the market share for generic products, the best choice for the individual patient and for society must be weighed.

A vast majority of the respondents does believe that today’s system saves money for the individual and society. Finally, information provided by a doctor had a positive correlation with a high level of trust in generic medicines, while a low level of education increased the odds of a low level of trust. These results suggest that information is important and should focus on assuring that patients understand bioequivalence and generic substitution so that they, despite socio-economic status, can feel safe and receive full benefit of their treatment.
References


Table 1. The characteristics of the study populations and their average trust value. The data are displayed for each level of the studied variables for all respondents and stratified into low (trust ≤ 3) and high (trust > 3) trust in the bioequivalence of interchangeable medicines. Trust values are shown for the whole study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levels</th>
<th>Number of respondents</th>
<th>Trust value</th>
<th>Low trust</th>
<th>High trust</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n(%)</td>
<td>Median (mean)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>294 (40.9)</td>
<td>4.00 (3.92)</td>
<td>63 (21.4)</td>
<td>231 (78.6)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>425 (59.1)</td>
<td>3.75 (3.60)</td>
<td>148 (34.8)</td>
<td>277 (65.4)</td>
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<tr>
<td>Age</td>
<td>18-35</td>
<td>36 (5.0)</td>
<td>4.00 (3.97)</td>
<td>4 (11.1)</td>
<td>32 (88.9)</td>
</tr>
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<td></td>
<td>36-50</td>
<td>103 (14.3)</td>
<td>4.00 (3.80)</td>
<td>31 (30.1)</td>
<td>72 (69.9)</td>
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<td></td>
<td>51-65</td>
<td>207 (28.8)</td>
<td>3.75 (3.72)</td>
<td>63 (30.4)</td>
<td>144 (69.6)</td>
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<tr>
<td></td>
<td>66-80</td>
<td>321 (44.6)</td>
<td>3.75 (3.69)</td>
<td>103 (32.1)</td>
<td>218 (67.9)</td>
</tr>
<tr>
<td></td>
<td>81+</td>
<td>52 (7.2)</td>
<td>3.75 (3.75)</td>
<td>10 (19.2)</td>
<td>42 (80.8)</td>
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<tr>
<td>Education level</td>
<td>Elementary school</td>
<td>144 (20)</td>
<td>3.50 (3.46)</td>
<td>56 (38.9)</td>
<td>88 (61.1)</td>
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<td>High school</td>
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<td>4.00 (3.76)</td>
<td>62 (26.7)</td>
<td>170 (73.3)</td>
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<td></td>
<td>University</td>
<td>341 (47.4)</td>
<td>4.00 (3.83)</td>
<td>92 (27.0)</td>
<td>249 (73.0)</td>
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<tr>
<td></td>
<td>Missing</td>
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<td>3.13 (3.13)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Income</td>
<td>&lt;10 000 SEK</td>
<td>71 (9.9)</td>
<td>3.75 (3.51)</td>
<td>26 (36.6)</td>
<td>45 (63.4)</td>
</tr>
<tr>
<td></td>
<td>10 000-19 999</td>
<td>247 (34.4)</td>
<td>3.75 (3.69)</td>
<td>75 (30.4)</td>
<td>172 (69.6)</td>
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<tr>
<td></td>
<td>20 000-29 999</td>
<td>135 (18.8)</td>
<td>4.00 (3.80)</td>
<td>34 (25.2)</td>
<td>101 (74.8)</td>
</tr>
<tr>
<td></td>
<td>30 000-39 999</td>
<td>105 (14.6)</td>
<td>4.00 (3.90)</td>
<td>22 (21.0)</td>
<td>83 (79.0)</td>
</tr>
<tr>
<td></td>
<td>40 000+</td>
<td>93 (13.5)</td>
<td>4.25 (3.94)</td>
<td>23 (24.7)</td>
<td>70 (75.3)</td>
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<td>3.38 (3.39)</td>
<td>31 (45.6)</td>
<td>37 (54.4)</td>
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<td>3.75 (3.75)</td>
<td>195 (27.9)</td>
<td>474 (72.1)</td>
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<tr>
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<td>Other</td>
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<td>3.75 (3.48)</td>
<td>15 (33.3)</td>
<td>30 (66.7)</td>
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<td>Missing</td>
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<td>3.50 (3.25)</td>
<td>1 (20.0)</td>
<td>4 (80.0)</td>
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<tr>
<td>Number of pharmaceuticals daily</td>
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<td>101 (14.0)</td>
<td>4.00 (3.64)</td>
<td>35 (34.7)</td>
<td>66 (65.3)</td>
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<td></td>
<td>1 to 2</td>
<td>261 (36.3)</td>
<td>3.75 (3.78)</td>
<td>66 (25.3)</td>
<td>195 (74.7)</td>
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<td>3 to 4</td>
<td>200 (27.8)</td>
<td>3.75 (3.73)</td>
<td>63 (16.5)</td>
<td>137 (83.5)</td>
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<td></td>
<td>5+</td>
<td>157 (21.8)</td>
<td>3.75 (3.72)</td>
<td>47 (30.0)</td>
<td>110 (70.0)</td>
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<tr>
<td>Total</td>
<td></td>
<td>719 (100.0)</td>
<td>3.75 (3.73)</td>
<td>211 (29.3)</td>
<td>508 (70.7)</td>
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</table>
Table 2. Overview of the answers to questionnaire items and average trust in bioequivalence. Data are displayed for each level of the studied variables for all respondents and stratified on low (trust≤3) and high (trust>3) trust in the bioequivalence of interchangeable medicines. Trust values are shown for the whole study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levels</th>
<th>Number of respondents</th>
<th>Trust</th>
<th>Low trust</th>
<th>High trust</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n(%)</td>
<td>Median (mean)</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>Acceptance of generic substitution (GS)</td>
<td>Sometimes/often/always Yes to GS</td>
<td>584 (81.2)</td>
<td>4.00 (3.96)</td>
<td>112 (19.2)</td>
<td>472 (80.8)</td>
</tr>
<tr>
<td></td>
<td>Seldom/never Yes</td>
<td>126 (17.5)</td>
<td>2.75 (2.68)</td>
<td>94 (74.6)</td>
<td>32 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Missing values</td>
<td>9 (1.3)</td>
<td>3.00 (3.39)</td>
<td>5 (55.6)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Previous experiences</td>
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**Table 3.** The result from the univariable (simple) logistic regression in the form of odds ratios (OR) for low trust with 95% confidence intervals. *p<0.05  **p<0.01  ***p<0.001

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<td>Seldom/never Yes</td>
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