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Original Research

Swedish patients' trust in the bioequivalence of interchangeable generics. What factors are important for low trust?

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Abstract

Background: Generic substitution (GS), is a cost-containment strategy meant to contain pharmaceutical expenditure without compromising health objectives. In order to shape GS into a policy that is both efficient and safe it is crucial to understand which factors are most important for patients' trust in GS.

Objective: To assess Swedish patients' level of trust in the bioequivalence of cheap and expensive generic medicines, and the association between trust and various factors.

Methods: A cross-sectional study was conducted. Questionnaires were handed out at 12 community pharmacies in Sweden, selected through stratified sampling, between March and April 2015. The questionnaire included seven socio-demographic questions in addition to 18 items divided into three sections: the 'views on generic medicine'-scale, information on and prior experiences of GS, financial aspects and change of color/name. Odds Ratios (ORs) were estimated applying adjusted logistic regression analyses with trust in the bioequivalence of generic medicines used as outcome variable and various factors as predictors.

Results: A total of 719 patients participated (response rate 85.7%). The results show that 70.7% of the respondents' trust that cheap and expensive interchangeable generic medicines are equal. Of the respondents 36.0% considered the change in appearance and 40.8% the change in names to complicate adherence. Lower trust in the bioequivalence of generic medicines were associated with being female (aOR=1.82, 95%CI 1.20:2.75, p<0.01), patients perceiving that changes in product name and appearance make adherence more complicated (aOR=2.18, 95%CI 1.48:3.19, p<0.001), disagreeing in that GS saves money for me (the customer) (aOR=2.68, 95%CI 1.58:4.55, p<0.001) or that GS saves money for society (aOR=3.21, 95%CI 1.46:7.08, p<0.01).

Conclusions: Seven out of ten respondents had trust in the bioequivalence of generic medicines, and one in three considered GS to complicate adherence. Four factors were associated with lower trust in GS, i.e. female gender, agreeing that changes in product name and appearance complicates adherence, disagreeing in that GS saves money for me or disagreeing in that GS saves money for the society. Low trust in GS needs to be addressed, not least in the communication between health professionals and patients.

Keywords

Drugs, Generic; Drug Substitution; Health Knowledge, Attitudes, Practice; Patient Preference; Multivariate Analysis; Surveys and Questionnaires; Sweden

INTRODUCTION

Generic substitution (GS), the substitution of prescribed medicines for cheaper generic alternatives, is a cost-containment strategy meant to contain pharmaceutical expenditure without compromising health objectives.[1] GS means that patients are offered a cheaper generic medicine with the same amount of active substance, same formula, with bioequivalence demonstrated in appropriate studies (thereby exchangeable) instead of the prescribed product.[2] It is implemented in a wide range of countries and the number of off-patent medicines entering the market is increasing.[1,3] GS was introduced in Sweden in 2002 and has been effective, lowering the cost of pharmaceuticals for patients and the government by billions (SEK) every year and giving Sweden among the lowest prices on off-patent medicines in all of Europe.[4]

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 accept GS and trust the generics they purchase from the pharmacy. Patients' experiences with GS are mixed. Nordic and international studies have reported that GS is well accepted by a majority of patients.[5,6] Nevertheless, patients report that GS confuses and worries them, possibly resulting in mix-ups, double medication and non-adherence thereby posing a risk to patient safety.[7-11] Some patients (range 8-34%) also report reduced effect of treatment or new side effects from GS.[5,12] Trust in the bioequivalence of generics

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has been proven important to receive the full benefit of a treatment.[13] Hence, patients' perceptions of the received product and trust in the bioequivalence of interchangeable generic and brand medicines can be crucial for adherence, effect and side effects.[13-15]

A systematic review from 2018 identified seven domains influencing generic use in the United States (patient-related; formulary management and cost containment; Medicare and Medicaid polices; promotional activities; educational initiatives; technological; and physician-related factors). Patient-related factors were the most studied and discussed domain in the identified litterature[16], implying its large role in understanding GS. Level of education, gender, prior experience with GS and income has been shown to influence patients' acceptance of GS.[5,16-21] Recommendations, information and the perceptions of physicians and pharmacists have also been found important to patients' experience and acceptance.[7,16,22-24] By including all those factors previously identified in one study, this study provides a broader knowledge base regarding patients' trust in the bioequivalence of generic medicines. This could benefit decision makers and professionals involved with the development and improvement of the current system for GS. The aim of this study was to assess Swedish patients' level of trust in the bioequivalence of cheap and expensive generic medicines, and the association between trust and various factors.

METHODS

Study design and context

This was a cross- sectional study with data collected through a structured questionnaire.[25]

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.[26] 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. 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 interchangeable.[27,28] 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.[1] The patient can also choose the prescribed product or an alternative generic instead of the generic with the lowest price, but will then have to pay the price difference out of pocket.

Sample selection

A stratified random sampling method was used.[25] All 290 municipalities in Sweden were divided into ten strata based on average yearly income (per household), which has been shown previously to influence patient preferences regarding generic substitution.[21] 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.[29] In the two strata with the highest number of inhabitants (representing more than 20% of the population), two municipalities were selected from each, resulting in 12 municipalities in total. One pharmacy was selected in each municipality with the aim of heterogeneity in regard to placement/surrounding and pharmacy owner. Proportionate sampling was used to decide the number of questionnaires for each stratum, so that the number of questionnaires per strata would reflect the total number of individuals in each strata and hence the population.[25] Questionnaires were hence handed out at 12 pharmacies in 12 different municipalities located in the northern, middle and southern part of Sweden. Inclusion criteria were that participants should have previously or currently use prescribed medicines, at some point have been offered a generic substitution and speak Swedish.

Questionnaire development

A questionnaire was developed based on previously identified factors relevant to patients' acceptance of and trust in generic substitution.[5,17,18,20,21] The questionnaire included 18 items divided into three sections, in addition to seven questions about socio-demographics. Section 1 consisted of the 'views on generic medicine'- scale with four items developed in Danish by Rathe *et al*. and one question regarding acceptance of GS.[30] The 'views on generic medicine'-scale consists of questions about the equivalence between cheaper and more expensive generics in regards to safety, side-effects and effect. The Danish questions were translated to Swedish by the Swedish and Danish authors (one author is fluent in both Swedish and Danish) and checked by experts in the field. The two languages are closely related and very similar in regard to the four items in the scale. All items were answered on a 5-point Likert response scale (strongly agree=5, agree=4, neutral=3, disagree=2, strongly disagree=1). The response to the four items-'views on generic medicine'- scale resulted in a trust index value from 1 to 5, which measured to what degree the patients considered interchangeable generics with different price (expensive/cheap) equal regarding safety, side-effects and effect. From here on described as trust in equality. 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. An average trust score was calculated of the 4 items (range 1 to 5) and dichotomized (low trust ≤3, and high trust>3) and applied as the outcome variable.

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

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included: age, gender, education level, native language, income, and number of medicines taken daily.

The questionnaire was initially tested for content validity by three researchers with wide experience in quantitative and qualitative method design. Subsequently, 20 cognitive interviews with concurrent and retrospective 'thinking aloud' and probing were carried out with medicine users focusing on comprehensiveness and relevance of the questions as well as the appearance of the questionnaire.[31] The questions and response scales were adapted accordingly. 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.

Data collection

All pharmacy owners and pharmacy managers at the 12 pharmacies contacted regarding data collection at or near the pharmacy agreed to participate. Pharmacy customers were approached consecutively inside or next to the entrance of the selected pharmacies. 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, for example due to poor eyesight. 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 customers. Data were therefore collected during all opening hours on weekdays as well as weekends.

Statistical analysis

In the analysis the following independent variables were used: gender, age, education level, income, native language, number of pharmaceuticals per day, acceptance of GS, information received, prior experiences with changes in effect/side effects, difficulties with adherence due to name and appearance changes and financial aspects. Moreover the two items regarding confusion because of changes in name or appearance were combined into one dichotomized item predicting overall confusion. All variables were initially analyzed descriptively. Socio-economic characteristics and the answers to section 2-3 are presented descriptively and stratified according to level of trust.

Crude and adjusted logistic regression analyses were performed. The crude association between low trust as the outcome variable and each of the independent variables

Table 1. The characteristics of the study population and their average trust in the bioequivalence of cheap and expensive interchangeable generic medicines. 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.

Variable	n (%)	**Trust value** (all respondents)			
		median	**mean (SD)**	**Low trust n (%)**	**High trust n (%)**
Gender					
Male	294 (40.9)	4.0	3.9 (0.9)	63 (21.4)	231 (78.6)
Female	425 (59.1)	3.8	3.6 (1.1)	148 (34.8)	277 (65.2)
Age					
18-35	36 (5.0)	4.0	4.0 (0.7)	4 (11.1)	32 (88.9)
36-50	103 (14.3)	4.0	3.8 (1.0)	31 (30.1)	72 (69.9)
51-65	207 (28.8)	3.8	3.7 (1.0)	63 (30.4)	144 (69.6)
66-80	321 (44.7)	3.8	3.7 (1.0)	103 (32.1)	218 (67.9)
81+	52 (7.2)	3.8	3.8 (0.9)	10 (19.2)	42 (80.8)
Education level					
Elementary school	144 (20)	3.5	3.5 (1.1)	56 (38.9)	88 (61.1)
High school	232 (32.3)	4.0	3.8 (1.0)	62 (26.7)	170 (73.3)
University	341 (47.4)	4.0	3.8 (0.9)	92 (27.0)	249 (73.0)
Missing	2 (0.3)	3.1	3.1 (1.6)	1 (50.0)	1 (50.0)
Income (monthly before tax)					
<10 000 SEK	71 (9.9)	3.8	3.5 (1.2)	26 (36.6)	45 (63.4)
10 000-19 999	247 (34.4)	3.8	3.7 (1.0)	75 (30.4)	172 (69.6)
20 000-29 999	135 (18.8)	4.0	3.8 (1.0)	34 (25.2)	101 (74.8)
30 000-39 999	105 (14.6)	4.0	3.9 (0.9)	22 (21.0)	83 (79.0)
40 000+	93 (9.5)	4.3	3.9 (0.9)	23 (24.7)	70 (75.3)
Missing	68 (9.5)	3.4	3.4 (1.2)	31 (45.6)	37 (54.4)
Native language					
Swedish	699 (93.0)	3.8	3.8 (1.0)	195 (27.9)	474 (67.8)
Other	45 (6.3)	3.8	3.5 (1.0)	15 (33.3)	30 (66.7)
Missing	5 (0.7)	3.5	3.3 (1.4)	1 (20.0)	4 (80.0)
Number of pharmaceuticals (daily)					
None	101 (14.0)	4.0	3.6 (1.1)	35 (34.7)	66 (65.3)
1 to 2	261 (36.3)	3.8	3.8 (0.9)	66 (25.3)	195 (74.7)
3 to 4	200 (27.8)	3.8	3.7 (1.0)	63 (16.5)	137 (68.5)
5+	157 (21.8)	3.8	3.7 (1.1)	47 (30.0)	110 (70.0)
Total	719 (100.0)	3.8	3.7 (1.0)	211 (29.3)	508 (70.7)

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was assessed through crude odds ratios (OR) with 95% confidence intervals (CI) applying univariable logistic regression. For the multivariable analysis the four items regarding 'prior experiences' were excluded due to a risk of overlap with questions in the trust index. The multivariable model was fitted by first including variables based on above univariate/crude analysis. Initially, variables with p-values <0.15 were included. In the next steps one by one, variables having a p-value >0.05 and implying a change less then <20 % in the beta coefficients by removal of the other variables in the remaining model were removed.[32] The fit of the model was tested with Hosmer and Lemeshow Test.[32]

RESULTS

A total of 849 pharmacy customers who met the inclusion criteria were invited to fill out the questionnaire; 719 agreed to participate, resulting in a response rate of 84.7%. The population characteristics and the median and average trust values are presented in Table 1. The majority of the participants were women (59.1%), the most common age group was 66-80 years old (44.7%) and most common education level was university or equivalent (47.4%). 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 3.8 (median) or 3.7 (mean, SD 1.0), see Table 1. The average

Table 2. Overview of the answers to questionnaire items and average trust in the bioequivalence of cheap and expensive exchangeable generic medicines. Data are displayed for each level of the studied variables for all respondents and stratified on low (trust≤ 3) and high (trust>3) trust.

Variable		Trust value (all respondents)		
	n (%)	Median (mean)	Low trust n (%)	High trust n (%)
Acceptance of generic substitution (GS)				
Sometimes/often/always Yes to GS	584 (81.2)	4.0 (4.0)	112 (19.2)	472 (80.8)
Seldom/never Yes	126 (17.5)	2.8 (2.7)	94 (74.6)	32 (25.4)
Missing values	9 (1.3)	3.0 (3.4)	5 (55.6)	4(44.4)
Previous experiences				
Have experienced better effect	132 (18.4)	3.4 (3.4)	58 (43.9)	74 (56.1)
Never experienced better effect	522 (72.6)	4.0 (3.9)	119 (22.8)	403 (77.2)
Missing values	65 (9.0)	3.0 (3.2)	34 (52.3)	31 (47.7)
Have experienced less effect	213 (29.6)	3.0 (3.0)	126 (59.2)	87 (40.8)
Never experienced less effect	440 (61.2)	4.3 (4.2)	50 (11.4)	390 (88.6)
Missing values	66 (9.2)	3.0 (3.2)	35 (53.0)	31 (47.0)
Have experienced fewer side-effects	102 (14.2)	4.0 (3.9)	56 (54.9)	46 (45.1)
Never experiences fewer side-effects	546 (75.9)	3.0 (3.1)	119 (21.8)	427 (78.2)
Missing values	71 (9.9)	3.0 (3.2)	36 (50.7)	35 (49.3)
Have experienced more side-effects	159 (22.1)	3.0 (2.9)	103 (64.8)	56 (35.2)
Never experiences more side-effects	490 (68.2)	4.3 (4.1)	69 (14.1)	421 (85.9)
Missing	70 (9.7)	3.0 (3.2)	39 (55.7)	31 (44.3)
Information				
Have received info from physician	467 (65.0)	4.0 (3.7)	125 (26.8)	342 (73.2)
Have never received info from physician	252 (35.0)	3.8 (3.7)	86 (34.1)	166 (65.9)
Have received info from Pharm	713 (99.2)	3.8 (3.7)	209 (29.3)	504 (70.7)
Have never received info from Pharm	6 (0.8)	3.50 (3.5)	2 (33.3)	4 (66.7)
Have received info from physician and Pharm	465 (64.7)	4.0 (3.8)	124 (26.7)	341 (73.3)
Never received info from physician or Pharm	4 (0.6)	3.6 (3.6)	1 (25.0)	3 (75.0)
Confusion				
Change in appearance complicates adherence				
Strongly agree/agree	259 (36.0)	3.5 (3.6)	97 (37.5)	162 (62.5)
Neutral/disagree/strongly disagree	458 (63.7)	4.0 (3.8)	112 (24.5)	346 (75.5)
Missing values	2 (0.3)	2.1 (2.1)	2 (100.0)	0
Change in names complicates adherence				
Strongly agree/agree	293 (40.8)	3.5 (3.5)	115 (39.2)	178 (60.8)
Neutral/disagree/strongly disagree	424 (59.0)	4.0 (3.9)	94 (22.2)	330 (77.8)
Missing values	2 (0.3)	2.1 (2.1)	2 (100.0)	0
Financial aspects				
GS saves money for me (the customer)				
Strongly agree/agree/neutral	623 (86.6)	4.0 (3.8)	159 (25.5)	464 (74.5)
Disagree/strongly disagree	95 (13.2)	3.0 (3.1)	52 (54.7)	43 (45.3)
Missing values	1 (0.2)	4.8 (4.8)	0	1 (100)
GS saves money for society				
Strongly agree/agree/neutral	671 (93.3)	4.0 (3.8)	179 (26.7)	492 (73.3)
Disagree/strongly disagree	47 (6.5)	2.5 (2.8)	32 (68.1)	15 (31.9)
Missing	1 (0.2)	5.0 (5.0)	0	1 (100.0)
The pharmacy profits from GS				
Strongly agree/agree	116 (16.1)	3.3 (3.4)	50 (43.1)	66 (56.9)
Neutral/disagree/strongly disagree	602 (83.7)	4.0 (3.8)	161 (26.7)	441 (73.3)
Missing	1 (0.2)	5.0 (5.0)	0	1 (100.0)

Pharm=Pharmacist; GS= Generic substitution

trust value was lower among women than among 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 the total sample was stratified into groups of low and high trust, 70.7% of the respondents had high trust in the equivalence. A majority (82.1%) of the respondents sometimes, often or always accepts generic substitution, see Table 2. The trust average (mean) among this group was 4.0 (SD 0.9) compared to 2.8 (SD 0.8) among those who seldom or never accept substitution. A majority (53.1%) of the patients with low trust in bioequivalence still accepted substitution sometimes, often or always.

In Table 2 findings concerning information regarding GS from physicians and pharmacists and patients' prior experiences with GS are presented. Nearly one-third (29.6%) of the respondents had experienced less effect after substitution, and 22.1% more side effects. However, 18.4% had experienced a 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 65.0% had received information from a physician. Slightly more than one-third of the patients considered the change in appearance (36.0%) or name (40.8%) to complicate adherence. 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% disagreed or strongly disagreed. Regarding savings on a personal level 13.2% disagreed or strongly disagreed, see Table 2.

The multiple logistic regression (Table 3) showed that women had lower trust than men (ORadjusted=1.82, 95%CI 1.20:2.75, p<0.01), and that patients who considered GS to complicate adherence had a lower trust in the bioequivalence compared to patients who did not (ORadjusted=2.18, 95%CI 1.48:3.19, p<0.001). Patients disagreeing in that GS saves money for me (the customer) (ORadjusted=2.68, 95%CI 1.58:4.55, p<0.001) or that GS saves money for society (ORadjusted=3.21, 95%CI 1.46:7.08, p<0.01) had lower trust, as presented in Table 3. The Hosmer and Lemeshow Test support fit of the model (p=0.92). For the crude analysis, see Online Appendix.

DISCUSSION

The aim of this study was to assess Swedish patients' level of trust in the bioequivalence of cheap and expensive generic medicines, and the association between trust and various factors. Overall, the results show that a majority (70.7%) of the respondents' trust that cheap and expensive interchangeable generic medicines are equal in regard to quality, effect and side-effects and that 81.2% of the respondents sometimes/often or always accepted GS. A vast majority of the respondents does believe that today's system saves money for the individual and society. Out of the studied variables, female gender and opinions that changes in name and appearance make adherence more complicated, disagreeing in that GS saves money for me (the customer) or that GS saves money for society were seen to significantly increase the odds of low trust in the bioequivalence. We found no association for level of education, prior experience with GS (excluded in our adjusted analysis due to overlap with the outcome variable) and income, which earlier has been shown to influence patients' acceptance of GS.[5,16-20] However, level of education and income were important mediators in our final model.

This study implies that the majority of Swedish patients (70.7%) trust in the bioequivalence of interchangeable generics, however almost one third of the patients have a low level of trust. Nevertheless, a majority (53.1%) of the patients with a low level of trust in the equality still accepted generic substitution. A Finnish questionnaire study found that 80.9% of patients held the opinion that cheaper generics are equally effective and in Denmark a corresponding figure was 90.4%.[30,33] This result indicates that Swedish patients have a lower level of trust in the bioequivalence of cheaper generics than patients in

Table 3. The result from the univariate and multivariate logistic regression analyses presented as odds ratios (OR) for low trust in the bioequivalence of cheap and expensive interchangeable generics with 95% confidence intervals (95%CI). *p<0.05 **p<0.01 ***p<0.001. (n=648)

Variable	Crude OR (95%CI)	Adjusted OR[1] (95%CI) n=648
Gender		
Male (ref)	1	1
Female	1.96 (1.39:2.76)***	1.82 (1.20:2.75)**
Confusion		
Change in appearance/name complicates adherence		
Neutral/disagree/strongly disagree on item 3A+3B (ref)	1	1
Agree/strongly agree on item 3A+3B	1.98 (1.43:2.75)***	2.18 (1.48:3.19)***
Financial aspects		
GS saves money for me (the customer)		
Strongly agree/agree/neutral (ref)	1	1
Disagree/strongly disagree	3.53 (2.27:5.50)***	2.68 (1.58:4.55)***
GS saves money for society		
Strongly agree/agree/neutral (ref)	1	1
Disagree/strongly disagree	5.86 (3.10:11.08)***	3.21 (1.46:7.08)**

[1]A backward elimination stepwise selection model was performed. Only the variables included in the final model are presented. The final model is adjusted for education level, monthly income, age, numbers of medication, and information from the physician. Individuals were excluded from regression analyses if data was missing on covariates. The final adjusted model included 648 patients.
GS= Generic substitution

Denmark and Finland. The system for substitution varies between the three countries; Denmark appoint new products with the lowest price every fortnight compared to every month in Sweden, and every three months in Finland. Hence, no conclusion can be drawn regarding the influence of the duration of price period on patients' trust in bioequivalence.

Another variable previously shown to positively influence patients trust in GS is the pharmaceutical counselling at the pharmacy.[7,22-24] Pharmacists have an important role to play in securing the patients' confidence in generics and consequently adherence to generics. As our results show, several factors impact the trust level, such as gender and opinions that changes in name and appearance make adherence more complicated, disagreeing in that GS saves money for me (the customer) or that GS saves money for society. Pharmacists should be aware of these factors when counselling patients. Potentially the 'views on generic medicine'-scale could be used by pharmacists in the counselling session to identify patients with low trust in the bioequivalence of cheaper generics. Pharmacists need to be both knowledgeable about generics and transfer this information to patients. In addition, they need to use counselling skills, such as listening, and explore the individual patient's opinion about generics.

No comparative communication study between the Nordic countries exist, but in all the countries there are studies showing a need for increased counselling.[34-38] As an example a Swedish study found that little or no medical information is given in the interaction with the patient during dispensing at the pharmacy.38 Still in Swedish pharmacies, no more time was spent on medical information when GS occurred even though Swedish pharmacists had identified GS as a complicating factor for adherence.[39,40] Nevertheless, both in the Finnish and the Danish legislation it is explicit in the legal texts, that information about generics has to be given both in writing (on the label) and orally.[41] There is also a specific requirement that Finnish pharmacists must ensure that the patient is aware of the fact that the generic is replacing the previous brand. This is not the case for the Swedish legislation. To further explore the impact of counselling on trust, a Nordic comparative study is warranted.

The results also showed that about 30% have experienced less effect compared to about 20% who had experienced a better effect from their medication after a substitution. In addition, almost 25% of patients reporting more side effects compared to 14% of participants reporting fewer side effects. This is in line with previous studies reporting changes in effect and/or side effects after substitution.[5,7,8,12] However, to the best of our knowledge no one has previously studied occurrence of better effect and fewer side effects after GS.

Over one third of patients considered GS to complicate adherence, this was also associated with lower trust in the bioequivalence. Lower adherence due to changes in medicine appearances after GS has previously been shown by Kesselheim *et al*.[11,42] Requirements regarding equal appearance for all generics that are to be substituted could prevent unintentional interruption in medication use and mix ups. In Sweden there are no requirements regarding appearance in order for approval of bioequivalence (except for differences in size) and substitution.[43] Hence, GS can result in differences in e.g. color of the medicine. In this way, current legislation does not support patients' use of medicine in this regard, thereby potentially causing GS to complicate adherence. This could compromise the outcome of the treatment and hence needs to be addressed, also in the communication between health professionals and patients.

In this study, females have lower trust in GS compared to men, which is also reported elsewhere.[6,17-20] Women often view themselves as more sensitive to medicines compared to men.[44,45] This might have consequences for their trust in GS, making them more sensitive to side effects and effects/no-effects of generics. They also have slightly different health behavior compared to males. For example, females tend to use more medicines compared to men.[46] They also seek more information about medicines.[47,48] Depending on what information they seek and find this could either make them more reluctant or more positive to GS.

To conclude, although rigid requirements exist regarding the demonstration of bioequivalence in order to be eligible for GS[27,28,49], many patients still distrust that cheap and expensive generics are equal in regard to quality, effect and side-effects. With this study design, it is not possible to determine the direction of the causality between low level of trust and experienced differences. Still distrust in equality are noteworthy as patients' perceptions of received product and trust in the bioequivalence of generics and brand medicines has been found to be crucial for adherence, received effect and side effects.[13-15] This suggests that it is this important for health professionals and authorities to be aware of low trust among some patients as well as adherence challenges after GS. Health care professionals need to keep this in mind when communicating with patients, in order to provide the support needed to prevent non-adherence and feelings of insecurity among patients. Also, physicians or pharmacists have the option to refuse GS for patients in risk of mix-ups. It can however affect the cost of the prescribed medicine for the patient and availability since the pharmacy might not have all generics in stock. Further, many refusals of substitution could not only result in a direct increase of costs for the patient, but could also affect prices generally due to a reduced market share for the preferred product of the month. Guided by the result from this study authorities and policy makers should reflect on whether the requirements for substitution are sufficient, as changes in colors and names can complicate patient adherence. With limited resources available, the best choice for the individual patient and for society must always be weighed in order to achieve a fair and cost-efficient healthcare system that does not compromise health objectives.

The method used 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 regard to

questions.[50] Second, there was a high response rate (84.7%). However, some limitations need to be mentioned. The labor-intensive method of having data collectors hand out the questionnaires kept the number of pharmacies where data were collected quite low (n=12) which could have affected the representability. While the gender distribution in the study population was similar to the population medicine users in Sweden[51], there was an underrepresentation of young medicine users and people in the lowest income level[29,47], and an overrepresentation of people with a university degree or equivalent.29 Customers who declined participation most often gave lack of time as a reason, but some stated that they did not like questionnaires in general. 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. The 'views on generic medicines' scale has been used for Danish patients prior to this study. When changing the dichotomization as originally presented in 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% of Danish patients.[30] Further the translation process can have resulted in divergence from the original language. As all participants were explained the concept of generic medicines and the word bioequivalence was not used, the internal validity was secured. A cross-sectional design also limits the ability to draw any casual interference of the identified relationships. Here a longitudinal design is warranted.

CONCLUSIONS

Seven out of ten respondents trusted the bioequivalence of generic medicines, and one in three considered GS to complicate adherence. In addition, four factors were associated with lower trust in GS i.e. female gender, agreeing with changes in product name and appearance complicates adherence, disagreeing in that GS saves money for me and disagreeing in that GS saves money for the society. Low trust in GS needs to be addressed, not least in the communication between health professionals and patients. More than one in three respondents considered the changes in name or appearance to complicate their adherence, and about one-third had experienced a change in effect and number of side effects after a substitution. This could compromise the outcome of the treatment. It is important that health professionals are attentive to, prevent and address nonadherence, especially after GS.

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CONFLICT OF INTEREST

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