

The effect of generic switching on concerns about medicine and non-persistence among Danish adults in a general practice setting

A combined population-based questionnaire and register study

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THE 3 ORIGINAL PAPERS ARE

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1. INTRODUCTION

Generic substitution has been implemented in many countries for many years. Debates on effectiveness, concerns and possible negative consequences such as reduced compliance, increase in hospitalisation or therapeutic duplications are continuously ongoing.

Generic substitution means that one medical product is replaced by another containing the same active substance within a

therapeutically equivalent threshold (2). This is determined by pharmacokinetic parameters calculated for test versus reference with associated 90% confidence intervals. According to the Danish Institute for Rational Pharmacotherapy two drugs are considered to be bioequivalent, if the 90% confidence intervals for these ratios are between 0.8 and 1.25. Although two formulations may be considered bioequivalent at a population level, individuals may fall outside this range with some receiving higher or lower doses than expected (3-5). As a consequence of this, certain drug groups have narrowed limits (90% CI: 0.9 to 1.11) for the approval of generic substitution such as antiepileptics and immunosuppressants (6).

Generic substitution was implemented in Denmark in 1991 and represents 68% of the Danish drug consumption (7). Pharmacies are obliged to substitute a generic version of a drug, if the general practitioner (GP) has not explicitly stated that it should not be performed, or the patient insists on having the more expensive drug. In both cases, the patients have to pay the price difference (8). In some countries generic substitution is only regarding a switch from brand name to generic drug, while in Denmark generic substitution includes all types of switches between drugs containing the same active substance (2, 5, 8). In Denmark, drug prices are regulated every 14 days, a prescription always comprises the brand name, and prescription of the substance name is not allowed (7, 9). The Danish healthcare system is tax funded, providing free access to general practice, outpatient clinics and hospital care for all inhabitants irrespective of age, socioeconomic status and geographical residence. Reimbursement increases with patients' expenses for prescription medication (10).

For medicine users the substitution scheme involves changing from one medicine to another that has the same effect, only different with regard to name, appearance and price. A questionnaire survey showed that most of the patients had positive attitudes towards generic substitution if they could save money and that generic substitution did not represent any risk to drug safety (11). Studies have been made in an attempt to quantify the "brand loyal group". Costa-Font et al. found that only a minority (13%) of the population in Spain would refuse generics as substitutes for the originator, which is a small percentage compared to a study from the US showing that only 37.6% preferred to take generics (12, 13). Studies have shown that patients were more willing to accept generic medicines for minor illnesses and less

likely to accept generic substitution, when the illness was perceived to be more serious (14-16). Not all physicians think all interchangeable medicines are effective and safe, and studies have shown that this may influence their prescribing behaviour negatively towards generic medicines (17, 18). Generic substitution has over time caused scepticism regarding certain drug categories and their bioequivalent range, especially with regard to antiepileptic drugs (AED) and antidepressants (19-22). Clinical outcomes have been assessed after generic substitution of antiepileptic drugs and cardiovascular drugs. With regard to antiepileptic drugs, LeLorier et al. observed a higher tendency to switching back to branded medications among antiepileptic drug users compared to users of antihypertensives and antihyperlipidemics. Specifically switching to generic lamotrigine was associated with increased physician visits and hospitalisations (23). With regard to cardiovascular drugs, Kesselheim et al. showed that brand-name drugs were equivalent to their generic alternatives when using clinical outcomes like blood pressure control (24) and Van Wijk et al. did not find associations between generic substitution and cardiovascular disease-related hospitalisation compared with brand-name therapy (25). Gagne et al. showed, in a new-user cohort study of statin users, a reduction in hospitalisation for acute coronary syndrome or stroke for those with generic statins compared with brand statins (26).

The generic substitution scheme implies changing from one drug to another that may vary by brand name, form, size, colour and taste (27). Speculations have been raised as to whether these medication switches between generic brands or from brand-name drugs to generics or vice versa may cause patient concerns (28-30). Furthermore, a qualitative study indicated two general themes: 1) Problems in recognising the substituted medicine, and 2) Lack of confidence in the identical effect of the substitutable medicines (31). Interview and questionnaire studies have shown that some patients felt anxious and insecure about generic substitution and expressed uncertainty with regard to inferior quality of generic drugs compared with the original products (32-34). Moreover, an increase in side effect was observed among users of antiepileptic drugs, when switching from brand name to a generic version or switching between generic versions of a drug had taken place (22). Studies regarding generic substitution and concerns have often focused on general experiences with generic substitution, rather than investigating a specific generic switch from one generic medication to another. Further, the studies have typically focused on one specific drug group such as AEDs, antidepressants or antihypertensive drugs. A study has indicated that generic substitution may affect patients' concerns about their medicine differently dependent on drug categories, e.g. users of antidepressants were more concerned that a generic drug was less effective than the prescribed drug. However, that study was not designed to capture experiences related to generic substitution within specific drug groups (29).

Generic substitution has always been accompanied by concerns about the clinical equivalence in terms of safety and effectiveness and concerns on patient level. Another area of relevance is whether it has consequences for the medicine users' ability to continue treatment (25, 35).

Adherence and continuation of therapy may be viewed from different perspectives among physicians and patients. The physician gives patients a solution to a problem with a potentially helpful treatment based on scientific evidence and clinical skills. The patients bring their health beliefs based on experience, cul-

ture, personality, and family tradition which may be seen by physicians as the impediment to the solution (36). The term adherence represents the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider (37). The term persistence represents the time over which a patient continues to fill a prescription, or the time from the initial filling of the prescription until the patient discontinues refilling of prescription (38).

Research on generic substitution and adherence or persistence has often focused on one shift from a brand-name drug to a generic drug or on incident users whose prescription is substituted at their first redemption. Most of these studies could not demonstrate that generic substitution affected adherence negatively, although few studies have shown reduced persistence after generic substitution (25, 35, 39-42). A study on patients' beliefs about medicine showed that patients with stronger beliefs about medicine being harmful were less adherent (43). How these beliefs about medicine influence patients' persistence after generic switching has not been shown.

The hypotheses of this thesis were that patient characteristics such as age and treatment with many different drugs could be related to reluctance towards switching between generically substitutable drugs. The same applies to specific drug categories where physicians have been sceptical towards generic substitution in relation to patients treated with antiepileptic drugs. Secondly, patients who experience changes from one drug to another that may vary by brand name, form, size, colour and taste due to generic substitution may become more concerned about their medicine. Finally, we hypothesised that generic switches may influence patients' persistence with medicine, meaning that patient might stop taking their medicine due to the generic switches.

2. AIMS

Study I aimed to analyse associations between generic substitution and patients' gender, age, drug group, number of different drugs used by the patient, views on generic medicines, confidence in the healthcare system, beliefs about medicine, and experience with earlier generic substitution.

Study II aimed to investigate the possible association between a specific generic switch and patients' concern about their medicine.

And finally study III examined how generic switching influences persistence to long-term treatment with special focus on importance of patients' concerns and views on generic medicine.

3. MATERIAL AND METHODS

Setting

The study was conducted among 6000 medicine users who had redeemed generically substitutable drugs with general reimbursement in September 2008. The medicine users were identified through Odense PharmacoEpidemiologic Database (OPED) described below. It was designed as a combined cross-sectional questionnaire and register study and additionally a cohort study.

Data sources

THE DANISH CIVIL REGISTRATION SYSTEM

All Danish citizens with a permanent residence in Denmark are registered with the Danish Civil Registration System (CRS) and assigned a unique personal identification (civil registration num-

ber: CPR) number. For each individual the CRS contains information on name, gender, date of birth and citizenship. Further, the system is continuously updated with regard to each individual's vital status, place of residence, and marital status. The CPR number assigned to each individual can be used in all national registers and enables accurate linkage between all of them (44-47).

ODENSE PHARMACOEPIDEMIOLOGIC DATABASE

Odense Pharmacoepidemiological database (OPED) offers complete coverage of all prescriptions presented at community pharmacies within the former County of Funen since 1991 and the Region of Southern Denmark (1.19 million) since 2007 (48). For each prescription, OPED records information on the date the prescription was dispensed and details on the dispensed drug including ATC code (Anatomical Therapeutic Chemical (ATC) Classification System), brand name, registration holder (having the right to marketing) and importer or parallel importer. OPED also provides information on the different drugs dispensed. In the ATC system substitutable medicines have the same fifth-level code corresponding to the active substance or a combination of substances (49). The demographic data from OPED feature data on migration and vital status.

Prescription data were used to gather information on any recent generic switch (substitution of the index medicine) and on medicine use during the preceding 12 months, including earlier generic switches and treatment with many different drugs. For each person a single substitutable drug (the index drug) dispensed on a given date in September 2008 (index date) was selected.

QUESTIONNAIRE

The idea for the project was developed by the Danish Ministry of Health with the aim of clarifying the potential consequences of generic substitution. The research study was designed by Professor Morten Andersen, MD, PhD, Professor Jens Søndergaard, MD, PhD, GP, Master in European Ethnology Karen Elberg, PhD, and Pharmacist Annette Foged.

Prior to the development of the questionnaire, a qualitative interview study was conducted among users of antiepileptics, antidepressants and other substitutable drugs. The findings of the qualitative study were that generic substitution caused anxiety and problems recognising the medicines, and that patients distrusted effects and safety of generics (31).

The questionnaire was developed on the basis of a literature review based on 4 major concepts regarding generic substitution: adverse effects and inferior quality of the substituted drugs, generic substitutions' influence on compliance, patients' views and knowledge about generic substitution and healthcare professionals' views and knowledge about generic substitution (15, 24, 25, 27, 50-52). The widely used and validated "Beliefs about Medicine Questionnaire" (BMQ) developed by Professor Rob Horne was applied in the questionnaire (53). Furthermore, based on the literature review two ad hoc items used as a scale were formulated and applied in the studies; "views on generic medicine" and "confidence in the healthcare system".

The heading of the questionnaire was "Your experience with medicine". In the introduction the patient was asked to confirm data from OPED with regard to the index drug and the index date.

A brief explanation was given about generic substitution, that is, medicinal products containing the same active substance manufactured or imported by different companies. In continuation of this, "generic medicine" was introduced and is the term used in the questionnaire. However, no distinction was made between generic medicine and brand medicine in the questionnaire. The purpose of the questionnaire was to elucidate patients' experience with medicine and combine it with information from OPED on a single well-defined generic switch of the index drug. The questionnaire was adapted to the individual subject with reference to their specific drug (index drug) in every question and index date printed on the questionnaire. The patient had to confirm purchase of the index drug to be included in the study (Flowchart Study I)

Items were phrased to be readily understandable, so that persons regardless of literacy skills would be able to answer without difficulty and within a short time. The questionnaire comprised 21 groups of questions and six of them were scales. Only the scales were applied in the thesis. Four scales from the BMQ: General harm, General overuse, Specific concerns about medicine, and Specific necessity, the latter only used in a subsequent analysis. The BMQ was translated into Danish by means of a standardised forward-backward translation (54) and finally approved by Rob Horne. Furthermore, the two ad hoc constructed scales were applied: views on generic medicine and confidence in the healthcare system.

Prior to pilot testing, the questionnaire was discussed by a group of researchers with different academic and clinical backgrounds to assess face validity and content validity – "was the questionnaire measuring, what it was supposed to measure?" Then among the target population, that is medicine users purchasing their drug at community pharmacies, a qualitative pilot test was conducted. A total of 18 people accepted to be interviewed to test content validity, comprehensibility, acceptability and feasibility of the questionnaire. The pilot testing only led to minor changes in terms of language and comprehension. Internal consistency of the two ad hoc constructed scales used in the study was assessed using Chronbach α and was acceptable.

The questionnaires were mailed out in December 2008. A reminder was sent two weeks later. In the mailing process administrative errors occurred: (wrong address and returned by the postal service, missing confirmation on the purchase of the index drug and missing signature on the questionnaire), in which case the questionnaire was returned with a polite invitation to sign the questionnaire. The patients' own GP was asked whether it was appropriate to approach their patients. This is standard procedure when using data from OPED to approach patients. The GP's were offered the opportunity to exclude patients that should not be included in the study (e.g. patients with severe terminal disease or dementia).

Sampling procedures

The three studies were conducted among 6000 medicine users aged 20 years or older and living in the Region of Southern Denmark who had redeemed generically substitutable drugs with general reimbursement in September 2008. The medicine users were identified through OPED. The survey was stratified on three drug groups: 2000 users of antiepileptics, 2000 users of antidepressants and 2000 users of other substitutable drugs. The group of other substitutable drugs comprised a wide range of medicines used for long-term treatment. Some drug classes were excluded:

anti-infectives, insulin, dermatologicals, and drugs not commonly prescribed in general practice, e.g. parenterally administered drugs and cytostatics. A substitutable drug was defined as a medicinal product approved for generic substitution by the Danish regulatory authorities. Only prescriptions issued by GPs were included. For each patient, the focus was on one purchase of a generically substitutable drug (index drug) during September 2008 (index date). Patients with dose dispensing were excluded. OPED was used to obtain information on the patients' redemption during the preceding 12 months, including ATC code, brand name and date of purchase. This way we were able to assess drug switches probably due to generic substitution and the number of different drugs dispensed. By means of OPED data it was possible to conduct a cohort study comprising information on all purchased medicine during the following 12 months following the index date (study III). The cohort comprised users of antidepressants and users of antiepileptics.

Outcome variables

STUDY I

In Study I generic switch of the index drug was the outcome. A generic switch was defined as taking place if the patient had previously purchased a drug different from the index drug, but within the same ATC code as the index drug (index ATC code). This distinction between drug products was based on brand name, registration holder (having the right to marketing) and importer or parallel importer. Generic switch was a dichotomous variable: Yes or No.

STUDY II

In Study II the Specific Concerns about Medicine scale from the BMQ was used as outcome to measure beliefs about the index drug. It consists of six items and assesses concerns about prescribed medication on the basis of beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication, for example "it worries me that I have to take this medicine". The scale "Concerns about medicine" was a continuous variable measured on a 5-point Likert scale. A higher score meant a stronger belief in the concept described by the scale.

STUDY III

In Study III non-persistence was calculated as outcome. A treatment episode was considered discontinued, if the interval between two prescriptions exceeded a period covered by the number of tablets prescribed plus a grace period of 90 days. We assume the patients as a minimum take 1 tablet per day.

Independent variables

In all three studies the demographic variables age and gender were used. Age was categorised into the following groups: 20-29 years; 30-39 years; 40-49 years; 50-59 years; 60-69 years; and ≥ 70 years.

INDIVIDUAL VARIABLES OBTAINED FROM OPED

OPED data provided information on any redemption the preceding 12 months prior to the index date including the index ATC code and other ATC codes, i.e. ATC codes different from that of the index drug.

Experience with earlier generic switch within the index ATC code
Earlier generic switching within the index ATC code was categorised into two groups: none and ≥ 1 switches.

Experience with earlier generic switch within other ATC codes
Earlier generic switching within other ATC code was categorised into three groups: none, 1-4 switches and ≥ 5 switches.

Redemptions of the index drug within 1 year prior to index date
The variable was used to illustrate patients' history of redeeming the index drug 365 days before the index date. The variable was categorised into 5 groups: 2 redemptions, 3-4 redemptions, 5-6 redemptions, 7-8 redemptions and ≥ 9 redemptions.

Drug groups

The three-selected drug categories were also included in the analyses, representing users of antiepileptics, users of antidepressants and users of other substitutable drugs.

Number of different drugs

To characterise the pattern of drug use at individual level, information was obtained on the amount of different ATC codes. The number of different drugs was defined as the number of ATC codes different from the index ATC code at the fifth level purchased by the patient during 120 days prior to the index date. The decision of 120 days prior to the index date was based on literature assessing the time between prescription redemption, showing that package sizes often are 100 tablets (55).

INDEPENDENT VARIABLES OBTAINED FROM THE PATIENT QUESTIONNAIRE

BMQ – specific concerns about medicine

BMQ specific concerns are described above. The scale is an independent variable in Study III.

BMQ – general overuse and general harm

Beliefs about Medicine in General use two major themes – general overuse and general harm. The *general overuse* scale represents medicines as over-prescribed by doctors who place too much trust in them (four items), and the *general harm* scale comprises representation of medication as harmful, addictive, poisonous and the belief that people who take medicines should stop their treatment every now and again (four items) (53, 56). Each item in the BMQ scales was measured on a 5-point Likert response scale (strongly disagree to strongly agree). A higher score meant a stronger belief in the concept described by the scale. The two BMQ subscales were dichotomised (low: ≤ 3 , high >3) in line with previous studies (56, 57)

BMQ – specific necessity

BMQ specific necessity assess patients' beliefs about the necessity and efficacy of medicines prescribed for specific condition (five items), e.g., *my health in the future will depend on my medicines* (53, 56). Each item was measured on a 5-point Likert response scale (strongly disagree to strongly agree). A higher score meant a stronger belief in the concept described by the scale. The BMQ scale was dichotomised (low: ≤ 3 , high >3) in line with previous studies (56, 57)

Views on generic medicine

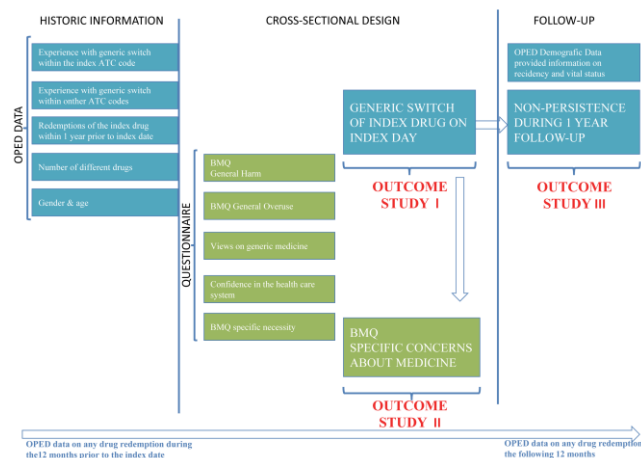
The scale *views on generic medicine* was specifically constructed for this questionnaire. The internal consistency of the scale was assessed using Cronbach's α (53). The scale was based on four items concerning side effects, quality and effectiveness of generic medicine (Chronbach's α : 0.88). Each item was measured on a 5-point Likert scale (1: strongly agree to 5: strongly disagree). A low score meant a positive view on generic medicine.

Confidence in the healthcare system

The scale *confidence in the healthcare system* was specifically constructed for this questionnaire. The internal consistency of the scale was also assessed using Cronbach's α . The scale was based on six items concerning confidence in the GP, the pharmacy, the hospitals and the healthcare authorities (Chronbach's α : 0.78). Each item was measured on a 5-point Likert scale (1: strongly agree to 5: strongly disagree). A high score meant a higher confidence in the healthcare system.

It was decided a priori to use similar dichotomisations of the scale as for the BMQ scales. Views on generic medicine (positive: ≤ 3 , negative >3) and confidence in the health care system (low confidence: ≤ 3 , high confidence >3).

Figure1: Illustrating Outcome variables for studies I, II and III and potential confounding variables



Missing data

If respondents had completed at least 60% of the scale a person's score was calculated as the average of the non-missing scale items. If less than 60% of the items were answered, the score was treated as missing.

Design

Study I and II are designed as a cross-sectional questionnaire survey combined with register data. Study III is designed as an observational cohort study – a combined population-based questionnaire and register study.

Statistical analyses

STUDY II

Generic switch was the outcome variable. As independent variables following variables were considered: gender, age, drug group, number of different drugs, earlier generic switch within the index ATC code and within other ATC codes, respectively, and each of the four scales *views on generic medicine*, *confidence in the healthcare system*, *BMQ general overuse* and *BMQ general harm*.

Age was categorised into six age groups. The BMQ subscales were dichotomised (low: ≤ 3 , high: >3) in line with previous studies (56, 57), and it was decided a priori to use similar dichotomisation of the scales *views on generic medicine* (positive ≤ 3 , negative >3) and *confidence in the healthcare system* (low confidence ≤ 3 , high confidence >3). The number of different drugs was categorised into three groups: 1 drug, 2-4 drugs and ≥ 5 drugs and was used as a proxy for comorbidity, as comorbidity may have influence on the choice of switching between generic versions of medicines or not.

To analyse associations between generic switching and each of the independent variables, crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using univariate and multiple logistic regression.

STUDY II

To analyse the association between *BMQ concerns about medicine* and generic switching, we used linear regression with specific concern score as outcome variable and generic switching of the index drug as independent variable. Possible confounding variables were processed in three models. The first model included the following possible confounding variables: gender, age, drug group, number of different drugs and earlier generic switch within the index ATC code and within other ATC codes. In the second model we added *views on generic medicine* as a possible confounder as it was negatively associated with generic switch in study I. In the final analysis we added the three scales, *BMQ general harm*, *BMQ general overuse*, and *confidence in the health-care system*, as they could be associated with generic switching and at the same time influence concerns about the index medicine.

Age was categorised into six groups. The two BMQ scales 'general harm' and 'general overuse' were dichotomised (low: ≤ 3 ; high: >3) and we decided a priori to use similar dichotomisations of the scales *views on generic medicine* (positive: ≤ 3 ; negative: >3) and *confidence in the healthcare system* (low confidence: ≤ 3 ; high confidence: >3). The 'number of different drugs' was categorised into three groups, 1, 2-4 and ≥ 5 drugs, and was used as a proxy for comorbidity, as comorbidity may influence concerns about medicine. Crude and adjusted results are presented with 95% confidence intervals (CIs).

STUDY III

In this study a subject was considered to be a medication user from the index date and for the subsequent number of days corresponding to the number of tablets of the prescription. A treatment episode was considered to have ended, if the interval between two prescriptions exceeded a period covered by the number of tablets prescribed plus a grace period of 90 days. It was assumed that patients as a minimum take 1 tablet per day. The grace period was introduced to allow for some degree of non-adherence and for irregular dispensing due to stockpiling. Information on migration and vital status of the cohort member was retrieved from the demographic data in OPED (48). We de-

defined non-persistence as the first episode during the study period, when a subject failed to present a subsequent prescription within the time window defined by the duration of the preceding prescription (58, 59).

To analyse associations between generic switching and non-persistence, Cox proportional hazards models were used to calculate Hazard Ratios (HRs) and corresponding 95% confidence intervals (CIs) and Kaplan-Meier curve to show time to non-persistence (38). In the Cox model adjustments were made for potential confounders such as age, gender, number of different drugs, concerns about medicine and views on generics. Sensitivity analyses were made, assessing the influence of gap length using periods of 30 days, 60 days, 90 days and 120 days. Another sensitivity analysis was made by using one stratum: on patients with a long history of using the index drug (≥ 3 redemptions before index date).

The analysis period was defined from the index date and 365 days ahead. Non-persistence was defined to take place, if the interval between two prescriptions exceeded a period covered by the number of tablets and a grace period of 90 days; the event was then registered on the day the number of tablets expired. An event was classified as such, if it took place within the 365 days of follow-up or before the patient moved out of the Region or died. Patients were censored on the day of death, date of moving or at the time the analysis period ended, if an event had not taken place. If censoring occurred during the grace period, the date of censoring was set to the day that the number of tablets expired.

P-values < 0.05 were considered statistically significant in Studies I, II and III. All statistical analyses were carried out using Stata Release 11.0 (Stata-Corp, College Station, TX, USA)

Ethical considerations

Written informed consent was obtained for all participants in order for their clinical records to be used in this study. According to the Act on Biomedical Research Ethics Committee System, the project was not a biomedical research project and therefore did not need the Research Ethics Committee's approval. The anonymity of patients was strictly preserved throughout the data entry and analysis process. The study was approved by the Danish Data Protection Agency (journal number 2008-41-2364).

Respondents were encouraged to contact the researchers by phone if they needed clarification or had any further questions. The respondents were informed that their responses were confidential.

4. RESULTS

Participants

A total of 6000 patients - 2000 users of antidepressants, 2000 users of antiepileptics, and 2000 users of other substitutable drugs - were invited to participate in the study. Of the 6000 patients identified, 385 patients (6.4%) were not eligible because of terminal disease or dementia. This was an assessment made by the patients' GPs. Of the 5615 patients eligible, 3040 did not return a signed questionnaire. In total 2575 patients responded. However, 99 patients did not confirm the purchase of the index drug as requested. In total 2476 of the 5615 eligible patients

returned the questionnaire and confirmed the index drug, yielding an overall response rate of 44.1%. The 2476 respondents were included in Study I, representing 736 users of antidepressants, 795 users of antiepileptic and 945 users of other substitutable drugs (Flowchart 1). Mean age for those who had experienced a generic switch on the index day was 57.8 years and 59.2 years for those who did not experience a generic switch on the index day. 60.2 % of the respondents were female and 39.8% were male (Table 1.1)

In Study II 204 respondents did not complete at least 60% of the scale according to the BMQ guideline. A total of 2217 were included in Study II (Flowchart 2). In Study III the cohort only comprised the users of antidepressants and users of antiepileptics. A total of 1368 patient were included in the analysis (Flowchart 3). During the analysis period 15 patients either moved out of the

Region of Southern Denmark or died and were therefore censored.

Table 1. Patient characteristics of respondents and non-respondents

	Returned, answered and signed				Total	
	Yes		No			
<i>Index drug</i>	N	%	N	%	N	%
Antiepileptics	828	45.1	1008	54.9	1836	100.0
Antidepressants	768	41.1	1102	58.9	1870	100.0
Other substitutable drugs	979	51.3	930	48.7	1909	100.0
<i>Age groups</i>						
20-39	271	37.6	449	62.4	720	100.0
40-49	398	45.1	484	54.9	882	100.0
50-59	580	51.0	557	49.0	1137	100.0
60-69	659	53.0	585	47.0	1244	100.0
≥ 70	667	40.9	965	59.1	1632	100.0
<i>Sex</i>						
Female	1551	46.2	1807	53.8	3358	100.0
Male	1024	45.4	1233	54.6	2257	100.0
Total	2575	45.9	3040	54.1	5615	100.0

Non-respondents

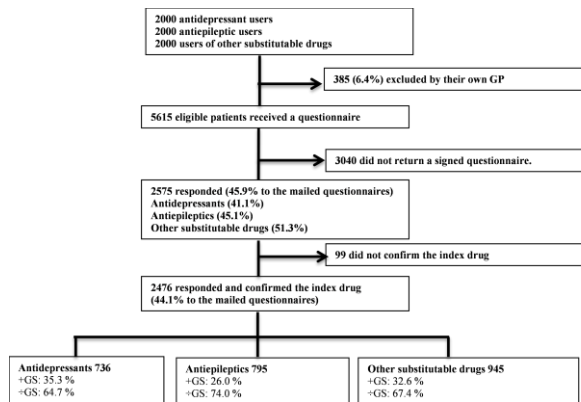
The distribution of age, gender and drug group of the non-respondents was quite similar to the distribution of the sample (Table 1), and there was no significant difference in the proportion of non-respondents among switchers and non-switchers (reference in the analysis), OR 0.81, 95% CI: (0.64;1.01).

Flowchart 1 of the study population of study I

Baseline patient characteristics

Among patients who had redeemed an antidepressant or "other substitutable drug" about one-third experienced a generic switch, while only one in four patients redeeming an antiepileptic experienced a generic switch (Flowchart 1). Baseline characteristics of the survey respondent are shown in Table 1.1 for the three drug-groups together, as well as for each drug group separately. Table 1.2 shows the baseline characteristics stratified according to whether or not the patients had experienced a generic switch.

Flowchart 1 of the study population of study I



Flowchart of the postal survey process.
 +GS: experienced a generic switch of the index drug on the index date.
 -GS: did not experience a generic switch of the index drug on the index date

Table 1 study I: Baseline characteristics of study population, stratified on drug groups

	Total N (%)	Antiepileptics N (%)	Antidepressants N (%)	Other substitutable drugs N (%)
<i>No. of patients (n=2476)</i>				
<i>Gender</i>				
Female	1491 (60.2)	448 (56.4)	520 (70.7)	523 (55.3)
Male	985 (39.8)	347 (43.7)	216 (29.4)	422 (44.7)
<i>Age</i>				
20-29	82 (3.3)	36 (4.5)	38 (5.2)	8 (0.9)
30-39	180 (7.3)	63 (7.9)	75 (10.2)	42 (4.4)
40-49	385 (15.5)	167 (21.0)	136 (18.5)	82 (8.7)
50-59	563 (22.7)	190 (23.9)	175 (23.8)	198 (21.0)
60-69	638 (25.8)	183 (23.0)	172 (23.4)	283 (30.0)
≥70	628 (25.4)	156 (19.6)	140 (19.0)	332 (35.1)
<i>Earlier generic switching index ATC code</i>				
None	1001 (40.4)	397 (49.9)	225 (30.6)	379 (40.1)
≥1 switches	1475 (59.6)	398 (50.1)	511 (69.4)	566 (59.9)
<i>Earlier generic switching other ATC code</i>				
None	561 (22.6)	180 (22.6)	187 (25.4)	194 (20.5)
1-4 switches	856 (34.6)	234 (29.4)	249 (33.8)	373 (39.5)
≥5 switches	1059 (42.8)	381 (47.9)	300 (40.8)	378 (40.0)
<i>Number of different drugs</i>				
1 drug	302 (12.2)	91 (11.5)	104 (14.1)	107 (11.3)
2-4 drugs	1006 (40.6)	305 (38.4)	307 (41.7)	394 (41.7)
≥5 drugs	1168 (47.2)	399 (50.2)	325 (44.2)	444 (47.0)
<i>Beliefs about medicines</i>				
General harm (low score) ^a	1893 (78.9)	634 (81.6)	552 (77.4)	707 (77.8)
General harm (high score)	506 (21.1)	143 (18.4)	161 (22.6)	202 (22.2)
<i>Beliefs about medicines</i>				
General overuse (low score) ^b	1632 (68.0)	543 (69.9)	464 (65.0)	625 (68.8)
General overuse (high score)	767 (32.0)	234 (30.1)	250 (35.0)	283 (31.2)
<i>Views on generic medicine^c</i>				
Positive	2032 (85.5)	608 (79.6)	625 (88.7)	799 (88.1)
Negative	344 (14.5)	156 (20.4)	80 (11.3)	108 (11.9)
<i>Confidence in healthcare system^d</i>				
Low confidence	276 (11.6)	113 (14.9)	86 (12.0)	77 (8.5)
High confidence	2102 (88.4)	646 (85.1)	629 (88.0)	827 (91.5)

^a General harm represents medication as harmful, addictive, poisonous and the belief that people who take medicines should stop their treatment every now again
^b General overuse represents medicines as over-prescribed by doctors who place too much trust in them
^c Views on cheaper generic medicine compared to more expensive medicine in terms of side effects, quality and effectiveness
^d Confidence in the healthcare system in terms of confidence in the GP, the pharmacy, the hospitals and the healthcare authorities

The median age was 57.8 years for the generic switchers and 59.2 years for the non-generic switchers, and gender distribution was almost the same in the two groups. Among patients making a generic switch 85.8% had experienced an earlier switch within their index ATC code compared to only 47.6% among patients not making a generic switch.

Univariate and multivariate logistic regression analyses

Table 1.3 shows that earlier switches within the index ATC code were associated with experiencing a generic switch (adjusted OR: 5.93, 95 % CI: 4.70;7.49). Having had more than five earlier switches within other ATC codes reduced the odds of experiencing a generic switch (adjusted OR: 0.68, 95 % CI: 0.49;0.95). The same pattern was seen for 1-4 earlier switches within other ATC

codes, but this was only marginally significant (adjusted OR: 0.75, 95%CI: 0.56;1.00). Negative “Views on generic medicine” reduced the odds of experiencing a generic switch (adjusted OR: 0.67, 95 % CI: 0.49;0.91). The youngest age category of drug users was more likely to experience a generic switch compared to the 40-49-year-old drug users (adjusted OR: 2.46, 95 % CI:1.41;4.30). No associations were found between generic switch and gender, drug group, “Number of different drugs” and “General harm”, “General overuse” or “Confidence in the health care system”, respectively. Separate analyses were made for each of the three drug categories (Table 1.4). The strongest association between a generic switch and earlier switches within the index drug was found in the antiepileptic group (OR: 17.18, 95 % CI: 10.47;28.18). The association was weaker for the antidepressant group (OR: 3.23, 95 % CI: 2.20;4.73) and for “Other substitutable drugs” (OR: 5.82, 95 % CI: 4.11;8.23). The antidepressant group stands out from the two other drug groups when looking at the effect of having had more than five earlier switches within other ATC codes, which reduced the odds of experiencing a generic switch (adjusted OR: 0.56, 95 % CI: 0.33;0.97), and they had higher odds of experiencing a generic switch if they scored high in “General overuse” (OR: 1.48, 95 % CI: 1.07;2.05). Among the users of antiepileptics and antidepressants the youngest age group had higher odds of experiencing a generic switch compared to the reference age group (40-49-year-olds) (antidepressants OR: 2.83, 95 % CI: 1.35;5.94; and antiepileptics OR: 2.21, 95% CI: 1.02;4.77). Further, negative “views on generic medicines” reduced the odds of experiencing a generic switch for the two groups (antiepileptics OR: 0.37, 95 % CI: 0.23;0.60 and antidepressants OR: 0.53, 95 % CI: 0.31;0.91).

Table 1.2 study I: characteristics of study population stratified on whether or not a generic switch took place

	Generic switch N (%)	No generic switch N (%)
<i>No. of patients (n=2476)</i>		
<i>Gender</i>		
Female	467 (60.3)	1024 (60.2)
Male	308 (39.7)	677 (39.8)
<i>Mean age</i>	57.8	59.2
<i>Drug group</i>		
Antiepileptics	207 (26.7)	588 (34.6)
Antidepressants	260 (33.6)	476 (28.0)
Other substitutable drugs	308 (39.7)	637 (37.5)
<i>Earlier generic switching index ATC code</i>		
None	110 (14.2)	891 (52.4)
≥1 switches	665 (85.8)	810 (47.6)
<i>Earlier generic switching other ATC code</i>		
None	199 (25.68)	362 (21.28)
1-4 switches	264 (34.06)	592 (34.80)
≥5 switches	312 (40.26)	747 (43.92)
<i>Number of different drugs</i>		
1 drug	103 (13.29)	199 (11.70)
2-4 drugs	329 (40.63)	677 (39.80)
≥5 drugs	343 (44.26)	825 (48.50)
<i>Beliefs about medicines</i>		
General harm (low score) ^a	591 (79.33)	1302 (78.72)
General harm (high score)	154 (20.67)	352 (21.28)
<i>Beliefs about medicines</i>		
General overuse (low score) ^b	497 (66.71)	1135 (68.62)
General overuse (high score)	248 (33.29)	519 (31.38)
<i>Views on generic medicine^c</i>		
Positive	662 (90.44)	1370 (83.33)
Negative	70 (9.56)	274 (16.67)
<i>Confidence in healthcare system^d</i>		
Low confidence	78 (10.57)	198 (12.07)
High confidence	660 (89.43)	1442 (87.93)

^a General harm represents medication as harmful, addictive, poisonous and the belief that people who take medicines should stop their treatment every now again
^b General overuse represents medicines as over-prescribed by doctors who place too much trust in them
^c Views on cheaper generic medicine compared to more expensive medicine in terms of side effects, quality and effectiveness
^d Confidence in the healthcare system in terms of confidence in the GP, the pharmacy, the hospitals and the healthcare authorities

Table 1.3 Study I: Univariate and adjusted associations between generic switching and age, gender, drug categories, number of different drugs, views on generic medicines, confidence in healthcare system, general harm, general overuse, and experience with earlier generic substitution

	Univariate OR (95% CI)	Adjusted OR (95% CI) ^a
<i>No of patients (n=2476)</i>		
<i>Age</i>		
20-29	2.27 (1.40;3.70)**	2.46 (1.41;4.30)*
30-39	1.45 (0.99;2.12)	1.33 (0.87;2.03)
40-49	1.00	1.00
50-59	1.18 (0.88;1.57)	1.25 (0.91;1.72)
60-69	1.31 (0.99;1.73)	1.30 (0.95;1.79)
≥70	1.07 (0.80;1.41)	1.03 (0.74;1.45)
<i>Drug groups</i>		
Antiepileptics	0.73 (0.59;0.90)**	0.85 (0.66;1.08)
Antidepressants	1.13 (0.92;1.38)	0.97 (0.76;1.23)
Other substitutable drugs	1.00	1.00
<i>Earlier generic switching index ATC code (none)</i>		
≥1 switches	6.65 (5.32;8.31)***	5.93 (4.70;7.49)***
<i>Earlier generic switching other ATC code</i>		
None	1.00	1.00
1-4 switches	0.81 (0.65;1.02)	0.75 (0.56;1.00)*
≥5 switches	0.76 (0.61;0.94)*	0.68 (0.49;0.95)*
<i>Number of different drugs</i>		
1 drug	1.00	1.00
2-4 drugs	0.94 (0.72;1.23)	1.11 (0.80;1.56)
≥5 drugs	0.80 (0.61;1.05)	1.07 (0.72;1.60)
<i>Beliefs about medicines</i>		
General harm (low score)	1.00	1.00
General harm (high score)	0.96 (0.78;1.19)	0.94 (0.73;1.22)
<i>Beliefs about medicines</i>		
General overuse (low score)	1.00	1.00
General overuse (high score)	1.09 (0.91;1.31)	1.11 (0.89;1.38)
<i>Views on generic medicine^e</i>		
Positive	1.00	1.00
Negative	0.53 (0.40;0.70)***	0.67 (0.49;0.91)*
<i>Confidence in healthcare system</i>		
Low confidence	1.00	1.00
High confidence	1.16 (0.88;1.53)	1.09 (0.80;1.49)

A is adjusted for gender, age, drug group, "number of different drugs", earlier generic switching within same ATC code, earlier generic switching within other ATC code, "General harm", "General overuse", "Views on generic medicine" and "Confidence in the healthcare system" using logistic regression.
*p<0.05 **p<0.01 ***p<0.001

Study II: Patients' concern about their medicine after a generic switch

Baseline patient characteristics

A total of 2476 patients confirmed the purchase of the index medicine. However, because of missing values, we ended up with 2217 patients (Flowchart 2). Table 2.1 shows the baseline characteristics stratified according to whether or not the patients had experienced a generic switch on the index day. The group of generic switchers was on average slightly younger, and the gender distribution was fairly similar in the two groups. Among the group of generic switchers, 84.9% had experienced an earlier generic switch within the index ATC code compared with only 47.5% among the non-switching group. The patients' scores were fairly similar in the two groups with regard to 'general harm', 'general overuse' and 'confidence in the healthcare system'. The group of patients who experienced generic switching held a statistically significantly more positive view on generic medicines.

Table 1.4 Study I: Univariate and adjusted associations between generic switching and patient characteristics stratified on drug groups

	Antiepileptics N = 795		Antidepressants N = 736		Other substitutable drugs N = 945	
	Univariate OR	Adjusted OR (95% CI)	Univariate OR	Adjusted OR (95% CI)	Univariate OR	Adjusted OR (95% CI)
<i>Earlier generic switching, index ATC code (none)</i>						
≥1 switches	1.00	1.00	1.00	1.00	1.00	1.00
	16.71***	17.18 (10.47;28.18)***	3.24***	3.23(2.20;4.73)***	5.86***	5.82 (4.11;8.23)***
<i>Earlier generic switching other ATC code (none)</i>						
1-4 switches	1.00	1.00	1.00	1.00	1.00	1.00
≥5 switches	0.67	0.65 (0.40;1.06)	0.84	0.77 (0.49;1.20)	0.87	0.97 (0.64;1.46)
	0.89	0.93 (0.55;1.56)	0.62*	0.56 (0.33;0.97)*	0.82	0.93 (0.59;1.55)
<i>Number of different drugs</i>						
1 drug	1.00	1.00	1.00	1.00	1.00	1.00
2-4 drugs	1.09	1.14 (0.66;1.97)	1.00	1.05 (0.65;1.69)	0.81	0.79 (0.50;1.24)
≥5 drugs	1.02	1.15 (0.66;2.01)	0.81	0.94 (0.57;1.55)	0.70	0.67 (0.42;1.06)
<i>Beliefs about medicines</i>						
General harm (low score) ^a	1.00	1.00	1.00	1.00	1.00	1.00
General harm (high score)	0.72	0.73 (0.47;1.15)	1.24	1.37 (0.94;1.98)	0.88	0.88 (0.62;1.24)
<i>Beliefs about medicines</i>						
General overuse (low score) ^b	1.00	1.00	1.00	1.00	1.00	1.00
General overuse (high score)	0.86	0.87 (0.61;1.25)	1.40*	1.43(1.03;1.99)*	1.01	1.01 (0.74;1.36)
<i>Views on generic medicine^c</i>						
Positive	1.00	1.00	1.00	1.00	1.00	1.00
Negative	0.43***	0.38 (0.23;0.62)***	0.54*	0.55 (0.32;0.95)*	0.73	0.77 (0.48;1.22)
<i>Confidence in healthcare system^d</i>						
Low confidence	1.00	1.00	1.00	1.00	1.00	1.00
High confidence	1.06	1.09 (0.68;1.74)	1.03	1.06 (0.66;1.72)	1.38	1.40 (0.82;2.40)

Adjusted for gender, age and "number of different drugs" using logistic regression
*p<0.05 **p<0.01 ***p<0.001

Flowchart 2 of the study population of study II

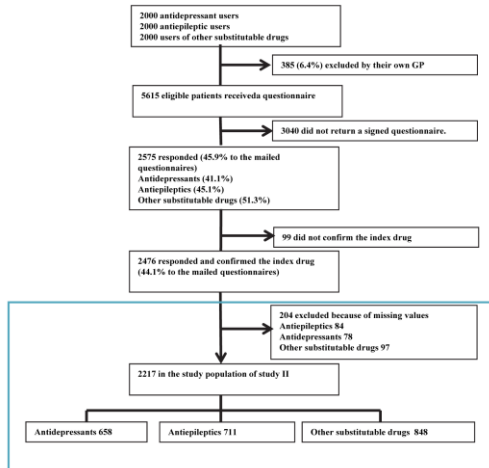


Table 2.1 Study II: Baseline characteristics of study population, stratified on whether or not a generic switch took place

	Generic switch N (%)	No generic switch N (%)
<i>No of patients (n=2217)</i>	689 (31.1%)	1528 (68.9%)
<i>Gender</i>		
Female	413 (60.0)	917 (60.0)
Male	276 (40.0)	611 (40.0)
<i>Mean age</i>	57.0 95% CI(55.9;58.1)	58.8 95% CI(58.0;59.5)
<i>Drug groups</i>		
Antiepileptics	183 (26.5)	528 (34.5)
Antidepressants	234 (34.0)	424 (27.8)
Other substitutable medicine	272 (39.5)	576 (37.7)
	100%	100%
<i>Earlier generic switching, index ATC code</i>		
None	104 (15.1)	802 (52.5)
≥1 switches	585 (84.9)	726 (47.5)
<i>Earlier generic switching, different ATC code</i>		
None	185 (25.9)	324 (21.2)
1-4 switches	242 (35.1)	540 (35.3)
≥5 switches	262 (38.0)	664 (43.5)
<i>Number of different drugs</i>		
1 drug	97 (14.1)	182 (11.9)
2-4 drugs	301 (43.7)	616 (40.3)
≥5 drugs	291 (42.2)	730 (47.8)
<i>Beliefs about medicines</i>		
General harm (low score) ^a	550 (79.8)	1211 (79.3)
General harm (high score)	139 (20.2)	317 (20.7)
<i>Beliefs about medicines</i>		
General overuse (low score) ^b	461 (66.9)	1047 (68.5)
General overuse (high score)	228 (33.1)	481 (31.5)
<i>Views on generic medicine^c</i>		
Positive	622 (90.3)	1271 (83.2)
Negative	67 (9.7)	257 (16.8)
<i>Confidence in healthcare system^d</i>		
Low confidence	71 (10.3)	184 (12.0)
High confidence	618 (89.7)	1344 (88.0)

^aGeneral harm represents medication as harmful, addictive, poisons and the belief that people who take medicines should stop their treatment every now again.
^bGeneral overuse represents medicines as over-prescribed by doctors who place too much trust in them.
^cViews on cheaper generic medicine compared with more expensive medicine in terms of side effects, quality and effectiveness.
^dConfidence in the healthcare system in terms of confidence in the GP, the pharmacy, the hospitals and the healthcare authorities.

Univariate and multivariate linear regression analyses

No statistically significant associations between concerns about the index medicine and the generic switch were found in any of the three models, Table 2.2. The difference in concerns between the two groups was -0.02, and mean concerns in the group of generic switchers were 2.72 (95% CI: 2.66; 2.78) and mean concerns in the group of non-switchers were 2.75 (95% CI: 2.71; 2.79). Among possible confounding variables we found that having had 1-4 earlier switches within other ATC codes led to marginally more concerns about the index medicine (0.13, 95% CI: 0.03; 0.22). This was, however, not the case when the patients had experienced more than five earlier generic switches. High

scores in both 'general harm' (0.39 95% CI: 0.30; 0.47) and 'general overuse' (0.28 95% CI 0.20; 0.35) were clearly associated with increased concerns about medicine.

Table 2.2 Study II: Univariate and adjusted associations between specific concerns about the index medicine and generic switching

	Univariate β (95% CI)	Adjusted β (95% CI) ^a	Adjusted β (95% CI) ^b	Adjusted β (95% CI) ^c
<i>No of patients (n=2217)</i>				
No generic switch	Ref	Ref	Ref	Ref
Generic switch	0.02 (-0.10;0.05)	-0.02 (-0.10;0.06)	Ref	Ref
<i>Earlier generic switching, index ATC code</i>				
None	Ref	Ref	Ref	Ref
≥1 switches	0.02 (-0.05;0.09)	0.03 (-0.04;0.10)	0.03 (-0.04;0.10)	0.04 (-0.03;0.11)
<i>Earlier generic switching, different ATC code</i>				
(none)	Ref	Ref	Ref	Ref
1-4 switches	0.12 (0.03;0.21)**	0.13 (0.03;0.23)*	0.13 (0.02;0.23)*	0.13 (0.03;0.22)*
≥5 switches	0.06 (-0.03;0.14)	0.03 (-0.09;0.15)	0.03 (-0.09;0.15)	0.06 (-0.05;0.17)
<i>Gender (female)</i>				
Male	Ref	Ref	Ref	Ref
Female	0.01 (-0.06;0.08)	0.02 (-0.05;0.09)	0.02 (-0.05;0.09)	0.05 (-0.02;0.12)
<i>Age (20-29)</i>				
30-39	Ref	Ref	Ref	Ref
40-49	0.11 (-0.11;0.33)	0.13 (-0.10;0.35)	0.13 (-0.09;0.35)	0.11 (-0.10;0.33)
50-59	0.09 (-0.13;0.31)	0.10 (-0.12;0.32)	0.10 (-0.12;0.32)	0.09 (-0.13;0.31)
60-69	0.19 (-0.01;0.30)	0.23 (0.03;0.43)**	0.23 (0.03;0.43)**	0.16 (-0.04;0.35)
≥70	0.23 (0.03;0.43)**	0.28 (0.07;0.48)**	0.28 (0.07;0.48)**	0.20 (0.01;0.40)*
<i>Drug groups (other substitutable drugs)</i>				
Antidepressants	Ref	Ref	Ref	Ref
Antiepileptics	0.14 (0.06;0.22)**	0.16 (0.08;0.25)**	0.16 (0.08;0.25)**	0.14 (0.06;0.22)**
Other substitutable drugs	0.16 (0.08;0.25)**	0.19 (0.10;0.27)**	0.18 (0.10;0.27)**	0.19 (0.10;0.27)**
<i>Number of different drugs</i>				
1 drug	Ref	Ref	Ref	Ref
2-4 drugs	0.06 (-0.05;0.17)	0.01 (-0.11;0.13)	0.00 (-0.11;0.13)	0.01 (-0.10;0.13)
≥5 drugs	0.05 (-0.06;0.16)	0.00 (-0.14;0.14)	0.00 (-0.14;0.14)	0.02 (-0.11;0.16)
<i>Beliefs about medicines</i>				
General harm (low score)	Ref	Ref	Ref	Ref
General harm (high score)	0.52 (0.43;0.60)**	0.52 (0.44;0.60)**	0.52 (0.44;0.60)**	0.59 (0.30;0.47)**
<i>Beliefs about medicines</i>				
General overuse (low score)	Ref	Ref	Ref	Ref
General overuse (high score)	0.41 (0.34;0.48)**	0.42 (0.35;0.49)**	0.42 (0.35;0.49)**	0.28 (0.20;0.35)**
<i>Views on generic medicine</i>				
Positive	Ref	Ref	Ref	Ref
Negative	0.03 (-0.02;0.13)	0.02 (-0.07;0.12)	0.02 (-0.07;0.12)	-0.004 (-0.10;0.09)
<i>Confidence in healthcare system</i>				
Low confidence	Ref	Ref	Ref	Ref
High confidence	0.25 (0.26;0.14)**	0.25 (0.26;0.14)**	0.25 (0.26;0.14)**	-0.16 (-0.27;-0.06)**

^aModel A: adjusted for experience with earlier generic switching (index ATC code and different ATC code), age, drug groups & number of different drugs.
^bModel B: adjusted for experience with earlier generic switching (index ATC code and different ATC code), gender, age, drug groups, number of different drugs.
^cModel C: adjusted for experience with earlier generic switching (index ATC code and different ATC code), gender, age, drug groups, number of different drugs.
^dViews on generic medicines.
 Ref: Refers to medicines - General overuse - General harm - Confidence in the healthcare system

Stratified analyses

Looking at the three drug groups, the users of antidepressants and users of antiepileptics were significantly more concerned about their index medicine than the group of users of other substitutable drugs. No associations were found between specific concerns about the index medicine and earlier switching within the index ATC code, number of different drugs or views on generic medicines. High confidence in the healthcare system was associated with less concern.

In the stratified analysis of drug categories, antidepressants, antiepileptics and other substitutable drugs, no statistically significant associations between concerns about medicine and the generic switch were found (Table 2.3). The clearest associations continue to be between increased concerns about the index medicine and 'general harm' and 'general overuse', respectively. There was no consistent pattern of the confounder variables.

Table 2.3 Study II: Adjusted associations between BMQ specific concern about the index medicine and patients characteristics stratified on drug groups

	Antiepileptics N: 711	Antidepressants N: 658	Other substitutable drugs N: 848
	Adjusted β (95% CI)	Adjusted β (95% CI)	Adjusted β (95% CI)
Generic switch (none)			
Generic switch	0.07 (-0.09;0.22)	-0.10 (-0.23;0.03)	-0.03 (-0.14;0.08)
Earlier generic switching, index ATC code (none)			
≥ 1 switches	-0.05 (-0.19;0.09)	0.001 (-0.13;0.13)	0.10 (-0.01;0.20)
Earlier generic switching, other ATC code (none)			
1-4 switches	0.21 (0.02;0.40)*	0.10 (-0.07;0.28)	0.06 (-0.09;0.21)
≥ 5 switches	0.09 (-0.12;0.30)	0.02 (-0.20;0.25)	0.03 (-0.14;0.21)
Gender (female)			
Male	0.01 (-0.11;0.14)	-0.002 (-0.13;0.14)	0.13 (0.02;0.23)*
Age (20-29)			
30-39	-0.04 (-0.42;0.34)	0.37 (0.06;0.69)*	-0.07 (-0.63;0.48)
40-49	0.09 (-0.25;0.43)	0.26 (-0.03;0.55)	0.18 (-0.35;0.71)
50-59	0.02 (-0.31;0.36)	0.36 (0.07;0.65)*	0.08 (-0.44;0.60)
60-69	0.10 (-0.24;0.44)	0.26 (-0.03;0.56)	0.22 (-0.30;0.73)
≥ 70	0.02 (-0.33;0.37)	0.19 (-0.12;0.50)	0.12 (-0.40;0.64)
Number of different drugs			
1 drug			
2-4 drugs	0.18 (-0.05;0.41)	-0.13 (-0.33;0.07)	-0.02 (-0.20;0.17)
≥ 5 drugs	0.16 (-0.10;0.42)	-0.15 (-0.40;0.10)	0.06 (-0.15;0.26)
Beliefs about medicines			
General harm (low score)			
General harm (high score)	0.44(0.26;0.61)***	0.37(0.21;0.53)***	0.39(0.26;0.52)***
Beliefs about medicines			
General overuse (low score)			
General overuse (high score)	0.26(0.12;0.41)***	0.40(0.26;0.53)***	0.21 (0.09;0.32)***
Views on generic medicine			
Positive			
Negative	-0.04 (-0.20;0.11)	0.01 (-0.18;0.20)	-0.03 (-0.12;0.18)
Confidence in healthcare system			
Low confidence			
High confidence	-0.26(-0.44;-0.09)**	-0.09 (-0.27;0.10)	-0.08 (-0.26;0.09)

Adjusted for experience with earlier generic switching (index ATC code and different ATC code), gender, age, drug groups, number of different drugs, *views on generic medicines, **Beliefs about medicines - General Harm, Beliefs about medicines - General Overuse & *confidence in the healthcare system

Study III Generic switch and non-persistence among medicine users

Baseline patient characteristics

A total of 1368 patients who used antiepileptics and antidepressants were included in the analysis (Flowchart 3). During the analysis period 15 patients either moved out of the Region of Southern Denmark or died and were therefore censored. Table 3.1 shows the baseline characteristics according to whether the patients had experienced a generic switch stratified on drug categories. Many patients with positive views on generic medicine and patients with previous experience with generic switching within the ATC code were represented among switchers in both drug categories.

Univariate and multivariate logistic regression analyses

During the 365 days of follow-up 237 of the included patients (17.3%) became non-persistent to their treatment (Figure 2). Table 3.2 shows that patients who experience their first generic switch had a higher risk of non-persistence of the index drug over time; HR 2.98, 95% CI (1.81;4.89) compared to never switchers. Generic switching did not influence persistence considerably in those having previous experience with generic switching of the specific drug, HR 1.02 (95% CI: 0.72;1.43) and HR 0.98 (95% CI: 0.68;1.41), respectively, for those switching on the index day and those who did not switch on the index day. Figure 2 shows that the time to non-persistence differed according to the patients' experience with generic switching. Among first-time switchers 35.7% became non-persistent during the first year of follow-up. In contrast, among patients who had never experienced a switch, 14.2% became non-persistent. Among patients with previous experience with generic switching within the index ATC code, 15.0% became non-persistent if they switched on the index day and 15.1% if they did not switch on the index day.

Flowchart 3 of the study population of Study III

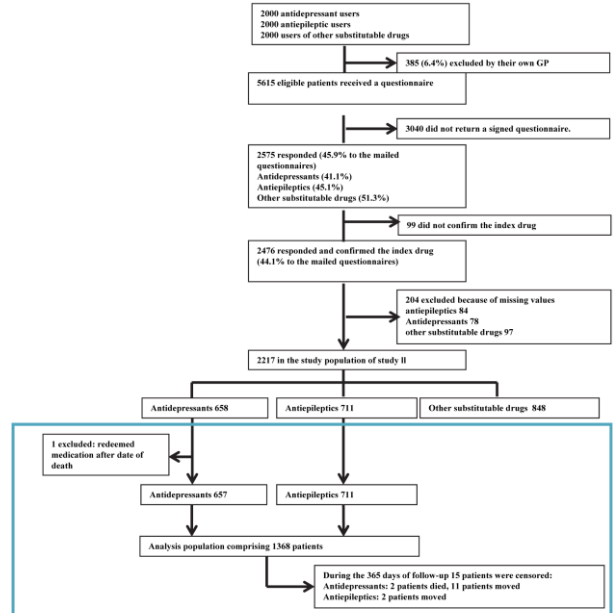


Table 3.1 Study III: Characteristic of the study population, stratified on whether a generic switch took place on the index day

Characteristics (N=1368)	Antiepileptics (N=711)		Antidepressants (N=657)	
	Generic switch N (%)	No generic switch N (%)	Generic switch N (%)	No generic switch N (%)
Earlier generic switching within the index ATC code	183 (25.7)	528 (74.3)	234 (35.6)	423 (64.4)
None	18 (10.2)	326 (64.3)	39 (17.3)	163 (39.7)
≥ 1 switches	158 (89.8)	181 (35.7)	187 (82.7)	248 (60.3)
Gender				
Male	75 (41.0)	256 (44.7)	64 (27.4)	127 (30.0)
Female	108 (59.0)	292 (55.3)	170 (72.6)	286 (70.0)
Age mean (SD)	54.2 (14.5)	56.4 (14.3)	54.4 (15.3)	55.9 (14.2)
Number of different drugs				
1 drug	23 (12.6)	60 (11.4)	36 (15.4)	62 (14.7)
2-4 drugs	73 (39.9)	202 (38.2)	109 (46.0)	173 (40.9)
≥ 5 drugs	87 (47.5)	266 (50.4)	89 (38.0)	188 (44.4)
Concerns about medicine (BMQ)				
Low score (not concerned)	114 (62.3)	341 (64.6)	152 (65.0)	259 (61.2)
High score (concerned)	69 (38.7)	187 (35.4)	82 (35.0)	164 (38.8)
Views on generic medicine				
Positive	163 (89.1)	404 (76.5)	215 (91.9)	365 (86.3)
Negative	20 (10.9)	124 (23.5)	19 (8.1)	58 (13.7)

Data are presented as the number (of subjects), with the percentage given in parenthesis.

The Cox regression analyses were also performed stratified on drug categories, i.e. antidepressants and antiepileptics, both showing higher risk of non-persistence when the patients experienced their first generic switch of the index drug. The group of antidepressant users had a HR of 2.19, 95% CI (1.21;3.96) and the users of antiepileptics a HR of 2.89, 95% CI (1.09;7.69) for non-persistence among first-time switchers versus never switchers. Interaction between the two drug categories was tested and no interaction was found.

Other potential confounding variables in the model such as age, concerns about medicine and views on generics had an effect on persistence. However, it did not affect our primary predictor considerably (Table 3.2).

Sensitivity analyses

The sensitivity analysis assessing the influence of gap length did not materially affect the association between switching patterns and non-persistence (Table 3.3).

Another subsequent analysis was conducted on patients with a long history of using the index drug by a stratified analysis on one stratum: patients with ≥ 3 redemptions before index date (N=1297). The analysis on patients having used the index drug for a long time

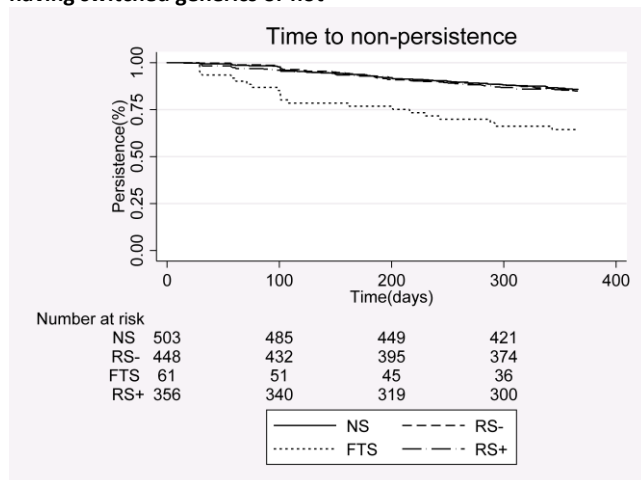
was similar to the main results comprising the entire study population, showing a higher risk of non-persistence when the patients experienced their first generic switch of the index drug HR 2.85 (1.34;6.07) compared to never switchers (Table 3.4)

Table 3.2 Study III: Hazard Ratio of non-persistence

Generic switch / earlier generic index date	switch index ATC	Univariate Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
No	No	1.00 (ref)	1.00 (ref)
No	Yes ≥1earlier switch	1.06 (0.76;1.49)	1.02 (0.72;1.43)
Yes	No	3.07 (1.88;5.00)***	2.98 (1.81;4.89)***
Yes	Yes ≥1earlier switch	1.07 (0.74;1.53)	0.98 (0.68;1.41)
Gender			
Female			
		1.00 (ref)	1.00 (ref)
Male			
		0.98 (0.74;1.30)	0.02 (0.77;1.37)
Age (years)			
20-29			
		1.00 (ref)	1.00 (ref)
30-39			
		0.48 (0.24;0.96)*	0.51 (0.25;1.03)
40-49			
		0.58 (0.32;1.04)	0.58 (0.32;1.06)
50-59			
		0.43 (0.24;0.79)**	0.45 (0.24;0.82)**
60-69			
		0.63 (0.35;1.11)	0.66 (0.36;1.21)
70+			
		0.48 (0.26;0.89)*	0.49 (0.26;0.95)*
Number of different drugs			
1 drug			
		1.00 (ref)	1.00 (ref)
2-4 drugs			
		0.89 (0.59;1.36)	0.91 (0.60;1.39)
≥5 drugs			
		0.86 (0.57;1.29)	0.93 (0.60;1.43)
BMQ specific concerns^a (low score)			
		1.00	1.00
High score			
		1.47 (1.11;1.93)**	1.54 (1.17;2.03)**
Views on generic medicine^c (positive)			
		1.00	1.00
Negative			
		0.66 (0.43;1.01)	0.65 (0.42;0.99)*

The adjusted model: adjusted for gender, age, number of different drugs, BMQ concerns and Views on generic medicine.
*p<0.05, **p<0.01 and ***p<0.001
^aBMQ specific concerns assesses beliefs about the index drug – it represents beliefs about the danger of dependence and long-term toxicity and disruptive effects of medication
^bViews on cheaper generic medicine compared with more expensive medicine in terms of side effects, quality and effectiveness.

Figure 2 study III: Kaplan-Meier plots of time to non-persistence having switched generics or not



NS: Never switchers, **RS-:** Recurrent Switchers without generic switch on index day, **FTS:** First Time Switchers and **RS+:** Recurrent Switchers with generic switch on index day

Table 3.3 Study III: Hazard Ratio of non-persistence with different length of grace periods

Generic switch / earlier generic index date	switch index ATC	Length of grace period (days)			
		30	60	90	120
No	No	1 (ref)	1 (ref)	1.00 (ref)	1 (ref)
No	Yes ≥1earlier switch	1.14 (0.86;1.50)	1.05 (0.77;1.45)	1.02 (0.72;1.43)	0.98 (0.68;1.41)
Yes	No	2.41 (1.55;3.74)***	2.81 (1.75;4.53)***	2.98 (1.81;4.89)***	2.67 (1.57;4.54)***
Yes	Yes ≥1earlier switch	1.21 (0.91;1.62)	1.01 (0.72;1.43)	0.98 (0.68;1.41)	0.99 (0.67;1.44)

Hazard ratios are presented as the full model described in Table 3.2
*p<0.05, **p<0.01 and ***p<0.001

Table 3.4 Study III: Hazard Ratio of non-persistence on patients with a long history of using the index drug

N=1297		Adjusted Hazard Ratio (95% CI)
Generic switch / earlier generic index date	switch index ATC	
No	No	1.00 (ref)
No	Yes ≥1earlier switch	1.34 (0.92;1.95)
Yes	No	2.85 (1.33;6.07)***
Yes	Yes ≥1earlier switch	1.30 (0.87;1.94)
BMQ specific concerns (low score)		1.00
High score		1.47 (1.09;1.98)*
Views on generic medicine (positive)		1.00
Negative		0.66 (0.41;1.07)

The 1297 patients were patients with ≥3 redemptions of the index drug before index date
The adjusted model: adjusted for gender, age, number of different drugs, BMQ concerns, BMQ necessity and Views on generic medicine.
*p<0.05, **p<0.01 and ***p<0.001

A final subsequent analysis was made adding the BMQ necessity to the adjusted Cox proportional hazard model. It did not have major impact on the estimate of the associations between generic switch variables and non-persistence (Table 3.5). The table shows that patients with a high score of necessity of the specific drug were positively associated with persistence. Three patients were excluded in Table 3.5 due to missing values in the BMQ necessity scale; N=1365. However, it did not influence the number of patients who became non-persistent during the 365 days of follow-up.

Table 3.5 Study III: Hazard Ratio of non-persistence including BMQ specific necessity as independent variable

N=1365		Adjusted Hazard Ratio (95% CI)
Generic switch / earlier generic index date	switch index ATC	
No	No	1.00 (ref)
No	Yes ≥1earlier switch	1.05 (0.75;1.48)
Yes	No	2.25 (1.36;3.72)**
Yes	Yes ≥1earlier switch	0.95 (0.66;1.36)
BMQ specific concerns^a (low score)		1.00
High score		1.64 (1.25;2.17)***
BMQ specific necessity^b (low score)		1.00
High score		0.27 (0.21;0.36)***
Views on generic medicine^c (positive)		1.00
Negative		0.76 (0.49;1.18)

The adjusted model: adjusted for gender, age, number of different drugs, BMQ concerns, BMQ necessity and Views on generic medicine.
*p<0.05, **p<0.01 and ***p<0.001
^aBMQ specific concerns assesses beliefs about the index drug – it represents beliefs about the danger of dependence and long-term toxicity and disruptive effects of medication
^bBMQ specific necessity assess patients' beliefs about the necessity of preventer medication for maintaining present and future health
^cViews on cheaper generic medicine compared with more expensive medicine in terms of side effects, quality and effectiveness.

5. DISCUSSION

Main findings

Study I showed that patients who had once experienced a generic switch were more likely to accept a future switch. This effect, however, appeared to be drug-specific, indicating that patients may accept generic substitution for some, but not all drugs used. Younger age was positively associated with making a generic switch, and negative views on generic medicine were negatively associated with making a generic switch.

For all three drug categories investigated, Study II showed that patients who experienced a generic switch did not have more concerns about their index medicine than patients without a generic switch.

Study III showed that patients who were first-time switchers of a specific drug were at higher risk of non-persistence versus never switchers or multiple switchers. Stratified analyses on drug categories showed higher risk of non-persistence for first-time switchers, both among users of antidepressants and users of antiepileptics.

These findings should be considered in relation to potential strengths and weaknesses of the study and in relation to other studies' findings.

Strengths and limitations

Several strengths and limitations need to be discussed in order to evaluate the internal validity (selection bias, information bias, and confounding) and external validity (generalisability) of the studies. These and other methodological issues are discussed in the following section.

Study design

The study was designed as a cross-sectional questionnaire survey and a register-based study in Studies I and II and a population-based cohort study in Study III. It provided an opportunity to determine possible factors associated with a generic switch and patient-related factors and concerns about medicine. A major strength of the cross-sectional design was that all questions in the questionnaire referred to the patients' index medicine by name, making the questions easier to relate to for the patient. Further, the patient had to confirm the purchase of the specific drug (index drug), which is the primary basis of the study and strengthened the validity of the questionnaire. Another strength of the three studies was that by means of prescription data focused on a single well-defined generic switch combined with information from a patient questionnaire.

Cross-sectional studies are limited by allowing only measurement of exposure and outcome variables at a certain point in time, and the design does not allow for the study of causality (60). The cross-sectional design offered some advantages by combining patient-reported attitudes and beliefs about medicine from the general population with register data.

Questionnaire surveys imply a possible weakness since the response rate is relative. The response rate of this study was 44.1%, which corresponds with other questionnaire survey studies (18, 61). The sample size was acceptable with a sufficient number in each drug category and among generic switchers and non-switchers, ensuring a high statistical precision of our estimates. The challenges for generalisability will be discussed later on.

The 1-year follow-up for subsequent drug purchase was achieved through register data. The cohort study design provides a non-self-reported measurement of persistence in the year following the index date, free of recall bias, by using gap analysis of dispensing and combining it with patient characteristics from the patient questionnaire.

Quality of the data sources

Register data

A strength of the study is its high internal validity due to the high quality of existing prescription data on one single well-defined generic switch, obtained by prescription data rather than self-reported information. In Study III OPED data provided the opportunity to address first-time switchers and recurrent switchers. OPED offers complete coverage on use of reimbursed drugs by all subjects. Death and emigration during follow-up were fully covered by the demographic part of OPED. To obtain reimbursement the pharmacies have an economic incentive to collect prescription data with as high accuracy as possible, securing a high level of data completeness (48, 62).

Another strength of all three studies is the population-based approach involving linkage data from regional registers, allowing individual-based longitudinal study of drug utilisation and associated factors, including characteristics from the questionnaire (48, 63).

Nonetheless, there are weaknesses using prescription data based on redeemed prescriptions. The distinction between physicians' prescribing and patients' non-persistence by use of prescription data is difficult. Primary non-adherence, where patients fail to fill the first prescription, could be more common among vulnerable patients, concerned patients, and patients with low income and this could affect the results of our study since those patients would not be eligible to the study according to the inclusion criteria (they had to purchase the index drug at least one time within 120 days prior to the index date). However, Pottegård et al showed that the overall rate of primary non-adherence among Danish residents in a general practice setting was low (overall 9.3%), the lowest rate of primary non-adherence was for drugs for the cardiovascular system (64). The study also assessed the length of time between the issuing of a prescription by the GP and the dispensing of the drug by the pharmacist, showing that most patients redeemed their prescription within the first week (64).

When using prescription data there is always the uncertainty as to whether a purchased drug is actually being used by the patient (65), and therefore researchers are left to examine surrogate measures of adherence or persistence behaviours by use of prescription data (66). Barat et al. assessed the agreement between patients' medication and their GPs' records, and omission occurred in a quarter of all cases (67). If the purchased drugs are bought to family members or bought to be stored at several locations (e.g. work or holiday home) in case of an urgent demand, this could be subject to misclassification of actual drug use resulting in an overestimation of the drug use prevalence. Despite the limitations, using prescription data is considered a valid method. Other methods could also have been possible, e.g. other studies use self-reported adherence, which seems to have moderate-to-high concordance with non-self-report measures of medication adherence (43, 68).

The OPED prescription database did not have information on prescribed daily doses, which would have been the ideal measure for continuity calculations. However, as tablets come in all clinically relevant strengths, it is unlikely that patients take less than one tablet per day, although there is a risk of underestimating our non-persistence outcome, when we assume patients only take one tablet per day.

Questionnaire

Ideally a fully validated instrument should have been used in order to secure accuracy of what the instrument was supposed to measure (69). It would be important with regard to determining the degree of confidence one can place on inferences based on scores from the scales. There are three main types of validity, including construct validity (the degree to which the content of a instrument is an adequate reflection of the construct to be measured) (70), content validity (whether the instrument samples all the relevant or important content or domains) and criterion validity (the correlation of a scale with some other measure of the concept under study, ideally a "gold standard" accepted and used in the field), which should be examined beforehand. Furthermore,

reliability testing (how reproducible the results of a scale are under different conditions) should have been explored (69).

A general weakness of questionnaire-based studies is that the respondents may understand or interpret the items differently than intended. In order to minimise this source of bias the validated BMQ was applied. As no existing questionnaires were identified in the literature search regarding views on generic medicine and confidence in the healthcare system, ad hoc scales were applied. In the validation process the content and construct validity was explored: First the questionnaire was discussed by a group of researchers with different academic and clinical backgrounds, then a qualitative pilot study was conducted and accordingly adjustments in items and formulations were made prior to the final questionnaire. The two ad hoc scales used in the studies had an acceptable internal consistency, tested by means of Chronbach's α .

In the three studies, questionnaire variables were alternately used as descriptive variables in Study I and adjusting variables in Studies II and III. The outcome in Study II was the specific concerns about medicine scale from the BMQ.

By using Beliefs about Medicine Questionnaire, which is an established instrument for assessing people's perceptions and expectations about medications, we had ensured good reliability and validity established in mentally and physical ill populations (53). This is consistent with a general practice setting, as BMQ has covered e.g. patients with diabetes, asthma, heart failure, users of statins and patients with mental illnesses (71).

In order to avoid response bias and diminish the influence of ordering effects, the BMQ items are not presented in conceptual order, meaning that items expressing the same view were not grouped together (56).

The focus of the questionnaire was patients' thoughts and concerns about medicine in general and specific concern about their index drug. A major strength of the study was that we asked the patients about their beliefs about medicine, views on generic medicine, and confidence about the healthcare system without asking them about a specified generic switch, thus the questions were independent of whether or not a generic switch had taken place.

The concept of BMQ is sometimes used as the "hidden determinant" of treatment outcome, and the theory is that patients' beliefs about medication affect their attitudes towards a particular treatment (72). BMQ has in particular been used as possible predictors of adherence to medication for chronic disorders (43, 73, 74). Studies have shown that patients with stronger beliefs about medicine as being harmful and with concerns about treatment were less adherent, while patients with stronger perceptions of necessity of treatment showed higher adherence (43, 71). The decision to use only the specific concerns about medicine from the BMQ scales in Study III was derived from Study II, having the main focus on the association between generic switch and non-persistence. The necessity-concerns framework would also have been an interesting approach to generic switch and non-persistence (71). However, a subsequent analysis was made and when BMQ necessity was added to the adjusted Cox proportional hazard model, it did not have major impact on the estimate of the associations between generic switch variables and non-persistence (data not shown).

Bias

Selection bias

The initial random sample was representative with regard to patients using generically substitutable drugs within 3 drug categories. However, we do not know to what extent the patients, who the GPs decided should not receive a questionnaire due to terminal disease or dementia (385 patients), would have had problems with generic substitution. One would expect that they could represent patients with concerns about generic substitution and imply a decline of generic substitution.

Patients' own experiences with generic substitution may also have influenced their decision about responding to the questionnaire. There is a possibility that some patients, who are already worried or distrustful about generic substitution, may decide not to accept generic substitution and some of them may not have the incentive to respond to the questionnaire, introducing a risk of underestimating concerns and non-persistence. On the other hand, patients who agree to generic switching and are not concerned about their medicine may also miss the incentive to respond to the questionnaire. The concerned patients or those who have experienced problems regarding generic substitution could be those with the biggest interest in participating in the survey.

The use of complete register data have minimised selection bias on exposure of generic substitution.

The study was by definition based on prevalent medication users. The inclusion criteria for this study was: "Patients were eligible for inclusion if they had made at least one other purchase of the same drug or one of its generic alternatives within 120 days prior to the index date". This fulfilled the criteria for persistence prior to the index date, where patients as a minimum have two redemptions within 120 days prior to index date (1: within 120 days and 2: purchase on the index date). This inclusion criterion implied that patients with a long history of using the index drug (≥ 3 redemptions) represented the majority of the study population ($N=1297$, 94.8 %). This could be a challenge for the external validity and will be discussed later on.

Information bias

A major strength of the studies was that by means of prescription data they focused on a single well-defined generic switch removing the risk of misclassification regarding generic switch. Additionally, information on previous generic switches, number of redemptions of the index drug and number of different drugs one year prior to the index date was also obtained by means of prescription data.

When looking at compliance studies, non-differential misclassification is difficult to avoid using prescription data since we do not know the patients' actual intake of medicine, unless qualitative interview studies are used which may then introduce interviewer bias (65). Mennickent et al suggested that a suitable measurement of compliance is to determine serum levels for evaluating patients' adherence to a specific drug (75). However, this is not feasible in large-scale studies, and further, this method may also imply uncertainties with regard to individual differences in pharmacokinetic properties (22).

In the 365 days of follow-up in Study III there was a risk that patients could recover from their disease or progression of the illness took place. Another possibility was that patients experienced adverse effects and the physician chose to prescribe a drug in another ATC group. It is important to stress that we had no information in our data on patients' or prescribers' initiatives. A

priori it was decided that these patients would have to be considered as non-persistent drug users, otherwise the research area would go beyond generic substitution and instead be medication changes between ATC codes. However, we considered it not to have a substantial influence on our primary result regarding the index drug, as the variation could take place in both groups of generic switchers and non-switchers.

Anecdotal memory may occur if patients are asked about generic substitution in general, far back in time, or if focusing on negative experiences with generic substitution (50, 76). The questions were not focused on whether the respondent had switched or not, or the difference between the current drug and the previously redeemed drug, because this could have introduced information bias. The relatively short interval between the drug purchase of the index drug and receiving the questionnaire probably minimised recall bias.

Confounding

Confounding may not be a part of the causal pathway. Confounding would be the confusion, or mixing of effects between the exposure and an unknown or unaccounted confounding factor, leading to masking or distortion of the true relationship between exposure and outcome (60).

As confounding factors, gender, age and number of different drugs were selected a priori. In addition in Studies I and II: drug group, earlier generic switching within the ATC code and within other ATC codes and each of the four scales: Views on generic medicine, Confidence in the healthcare system, General harm and General overuse were considered as possible confounding variables. In Study III Views on generic medicine and Confidence in the health care system were added as possible confounder variables.

Unmeasured confounding

We cannot exclude the possibility that unmeasured confounders could have influenced the results of the three studies.

Comorbidity and severity of disease could have been relevant to include considering confounding by severity. One of the hypotheses of the study was that patients treated with a high number of different drugs, which was used as a proxy for comorbidity, could be more reluctant towards generic switching and become more concerned about their medicine when a generic switch had taken place. Duh et al. applied the Charlson Comorbidity index on users of an antiepileptic drug, which showed a higher risk of hospitalisation for multiple-generic medication use compared to branded medication use (77). Though other co-morbidity indexes, e.g. the Charlson Comorbidity index, could have shown an association, such an effect was not found when the variable "Number of different drugs" was used as an independent variable in the regression models of the three studies.

Another possible potential confounder could be the "healthy adherer effect". Simpson et al. found that good adherence to placebo was associated with lower mortality compared with poor adherence to placebo, indicating that adherence might be a predictor of overall healthy behaviour (78). However, we find it unlikely that "healthy adherer" behaviour would predict a different pattern of persistence between patients who did or did not experience a generic switch.

Socioeconomic factors could also have had an impact on our result on the choice of making generic switches, which could indirectly influence whether patients stay persistent with their treatment, as generic switch was associated with non-

persistence. Studies have shown that educational attainment had a direct relationship with having correct knowledge of generics, which was a determinant for using generic medicines (12, 16). However, socioeconomic factors may influence the results in different directions. Iosifescu et al. observed that lower education and low income were associated with negative beliefs about generics (79). On the other hand, Drozdowska et al. showed that lower education and income were associated with an increased willingness to choose generics (80).

Discussion – statistics

Dichotomisation of questionnaire variables may lead to loss of information, providing less detailed information. However, in terms of making the interpretation as simple as possible, the BMQ and ad hoc constructed scales were dichotomised when used as independent variables. It is difficult to define what is the most appropriate cut-off point using dichotomisation. Examples in the literature suggest a cut-off point with a score >3 to be considered as having a high score (56, 57) and Nestoriuc et al. dichotomised BMQ specific concerns according to a median split (scores ≥ 17 were considered high) (81). Subsequent analyses could have been made including BMQ scales as continuous covariates; this method has been used in other studies (43, 73). Regarding BMQ variables 'Uncertain' was categorised as "low score", which may have underestimated the influence of perceiving medication as harmful and having concerns about medicine. Regarding views on generic medicine, those who were uncertain were categorised as positive, which may have underestimated the influence of perceiving generics as having less quality and effectiveness. And finally, patients who were uncertain about confidence in the healthcare system were categorised as having a low confidence, which may have overestimated the influence of having low confidence in the healthcare system.

Missing values

Some considerations were made about missing values in the questionnaire. Using Rob Horne's BMQ there is a specific threshold value of non-missing of 60-80% (56). Imputation would be a method to handle missing values, replacing them with the patient's average score of the other items in the scale. However, prior to the analysis process it was decided that if respondents had completed at least 60% of the scale, a person's score was calculated solely as the average of the non-missing scale items. If less than 60% of the items were answered, the score was treated as missing. This procedure was considered reasonable in the light of the validated BMQ scales with an expected high correlation within the items. To establish uniformity of the analyses of questionnaire items it was decided a priori to treat the ad hoc constructed items Views on generic medicine and Confidence in the healthcare system in the same manner. This was considered reasonable in light of the satisfying internal consistency within the scales.

Generalisability

The results from the three studies, comprising patients from a general practice setting, are considered to be generalisable to other regions in Denmark with respect to drug prescribing, reimbursement systems, healthcare services free of charge at the point of care, and general practitioner as gatekeeper. However, the challenges are different from one healthcare system to another across countries with regard to implementation of generic

substitution, generic prescribing and the availability of supply of generic medicine (82). Further, patient beliefs about medicine may differ across cultures. Hence, these differences could influence the results and affect the generalisability to other countries.

By including only patients with a relatively long history of using the index drug (prevalent medication users), there could be a risk of having a population with many persistent medication users compared with patients with newly started treatment, which could reduce the variation in our results. Tamblyn et al. showed that the rate of not filling prescriptions was greater for new users than for those who were switching treatment from one drug to another within a pharmacological class (83), and Fischer et al. observed a similar trend (84). However, the results from Study III showed that there was in fact variation in the study population with regard to non-persistence.

In the random sample selection patients with dose dispensing were excluded. They were not able to give informed consent to generic switching, thus our results do not apply on this population. Though dose dispensing may have possible sources of errors with disagreements between the medication prescribed by doctors and what is dispensed it is also considered to improve the quality of medication handling and medication safety (85, 86). Patients with dose dispensing could represent a vulnerable patient category. However, patients applying dose dispensing would probably not notice changes in form, size and colour and it would not be expected that generic switch would affect medication non-persistence in this patient category.

The response rate of 44.1% could imply that respondents and non-respondents could differ on other parameters, e.g. respondents could be more sceptical towards generic substitution than non-respondents. However, we have no evidence to support that. What we did find was that the distribution of age, gender and drug group of the non-respondents was quite similar to the distribution of the sample, and there was no significant difference in the proportion of non-respondents among switchers and non-switchers; hence we assume that our results are generalisable to the population of long term-drug users.

Comparison to other studies

The hypotheses of this thesis were that patient characteristics such as age and treatment with many different drugs could be related to reluctance towards switching between generically substitutable drugs. The same applies to specific drug categories, where physicians have been sceptical towards generic substitution for instance in relation to patients treated with antiepileptic drugs. Secondly, patients who experience changes from one drug to another that may vary by brand name, form, size, colour and taste due to generic substitution may become more concerned about their medicine. Finally, we hypothesised that generic switches may influence patients' persistence with medicine, meaning that patients might stop taking their medicine due to the generic switches.

Study I

In Study I possible associations between generic switch and patient characteristics were assessed.

The main finding was the positive association between a generic switch and experience with earlier generic switches within the same drug type, which is in line with previous research showing that familiarity with medicine is much more important than price to people who had refused generic substitution (87). Interesting-

ly, this tendency was not seen when looking at the patient's earlier switches within other drug types, which may indicate that attitudes towards generic switching are drug-specific.

Research has shown that use of generic medicines was lower, when the patient's illness was serious, indicating that attitudes towards generic medicine may vary across drug classes for different diseases, and that patients may accept generic substitution for some but not all drugs they use (14-16).

It was not surprising that patients having negative views on generic medicine were associated with less frequent generic switching, and it is in accordance with previous research showing that positive beliefs about generic substitution were associated with increased generic drug use (14, 61).

The study did not underpin our hypotheses that characteristics such as being elderly and being treated with many different drugs would make people more reluctant to switch between generically substitutable drugs.

It was expected that certain drug categories would be associated with reduced odds of making a generic switch. However, this effect was not found, not even for drug categories where physicians have been known to be sceptical towards generic substitution, especially regarding antiepileptics (88, 89) and where patients have reported breakthrough seizures and increased side effects after generic substitution of antiepileptic drugs (90). Though generic switching was less common for users of antiepileptics than for the other two drug categories, this was not statistically significant in the adjusted analysis. It is often specialists in neurology, who prescribe antiepileptics in the initial phase, and our results may reflect their scepticism towards generic substitution (20)

Study II

In Study II possible associations between generic switching and concerns about medicine were assessed. The study showed that patients who experienced a generic switch did not have more concerns about their index medicine than patients without a generic switch. The method of this study is different from previous studies by focusing on one single well-defined generic switch obtained by prescription data and the use of a validated psychometrical instrument. This implies that the results differ from previous interview and case-based studies, showing patient concerns and insecurity, and the reason for this may be the way the patients have been asked the questions (50). If the focus has been on general experiences about generic substitution or on negative experiences with generic substitution these studies may risk anecdotal memory.

In the section on selection bias it was discussed whether patients, who were already worried or distrustful about generic substitution, may have decided not to accept generic substitution and perhaps did not participate in the questionnaire survey. However, among respondents negative views on generic medicine were not associated with concerns about the index medicine, but negatively associated with generic switch. Adjusting for views on generic medicine had no impact on our results regarding concerns and generic switching. Furthermore, there was no difference in general beliefs about medicine between switchers and non-switchers, and adjustments for general beliefs had no impact on our result regarding concerns and generic switching. We know that decisions about taking medications are likely to be influenced by beliefs about medicines as well as beliefs about the illness, which the medication is intended to treat or prevent (53). The

clear association between specific concerns about the index medicine and BMQ general harm and general overuse underpins our primary results.

To some extent, this study's findings are at odds with previous studies, showing that a change in name, colour, form or taste when patients switch between two drugs is known to cause confusion and insecurity with respect to the difference between the old and the new products and perceived quality (34). However, patients did not become more concerned about their index medicine when they experienced a drug switch, nor did medication users who are known to be more reluctant towards generic substitution and also more likely to report adverse drug reactions, such as users of antidepressants and antiepileptics (20, 91, 92). There was a sufficient number in each drug category to detect relevant associations between concerns about medicine and generic switching in the three drug categories investigated. However, no variation between drug categories was found. A possible explanation could be that patients do not consider generic substitution to cause any risk to drug safety (11). The patients in this study may have become accustomed to generic substitution, or the patients might not even realise that they experience a generic switch. Toverud et al. showed that patients in general have great trust in their doctors (34), which is in line with this study showing that patients who had high confidence in the healthcare system, including the GPs, were less concerned about their index medicine. However, Toverud's study also showed that the patients did not feel sufficiently informed about being given a product different from the prescribed, when they went to the pharmacy (34). Study II indicates that generic substitution may be well explained to the patients by doctors in the Danish healthcare setting.

In conclusion, patients who experienced a generic switch did not have more concerns about their index medicine than patients without a generic switch. However, experience with generic switching had influence, showing that patients who had limited experience with generic switching within other ATC codes were more concerned about their index medicine than patients with more experience. Study I and Heikkilä et al. showed that experience with generic switching was important for acceptance of generic substitution (18). The results of Study II indicate that first-time switchers need more attention by doctors and pharmacists who handle generic substitution.

Study III

The hypothesis of study III was that generic switches might negatively influence patients' medication persistence.

The study showed that patients who were first-time switchers of a specific drug were at higher risk of non-persistence versus never switchers or multiple switchers. The stratified analyses showed higher risk of non-persistence for first-time switchers for both drug categories, i.e. antidepressants and antiepileptics.

This study adds to the body of knowledge about the mechanisms of non-persistence in a wide group of patients, both addressing first-time switchers and recurrent switchers. Previous studies have been based on rather selected patient sampling without a control group with regard to generic switching, where this study stands out due to having control groups differing on their level of experience with generic switches (27, 50). In addition, we obtained information on previous generic switches on the same specific drug within one year. In that way we had a unique opportunity to look into patients' overall experience with generic switching of one specific drug.

The choice of non-persistence rather than non-adherence (58) was made because of our interest in whether patients stay on their therapy, when a generic switch has taken place. The definition of non-persistence with a 90-day grace period was based on literature (58, 93, 94). For drugs such as antiepileptics and antidepressants missed doses may be more problematic and decrease the effectiveness of therapy compared to missed doses of other classes of drugs, e.g. antihypertensive agents, implying that a short grace period should be used (58). However, the sensitivity analyses showed robustness of the results irrespective of the length of the grace periods with results having the same direction with narrow confidence intervals.

There is consistency between this study's results and previous studies comprising incident medication users. Ström et al. found that patients who had their medicine substituted at their first prescription refill had a higher probability of discontinuing treatment (35). Kesselheim et al. also studied incident medication users, in this case users of anticonvulsants, and found that changes in pill colour or shape due to generic substitution were associated with discontinuation (42). The grace period employed was, however, only 5 days, which might have led to an overestimated rate of non-persistence. Studies pointing in other directions are e.g. Van Wijk et al. who assessed non-adherence among incident users of antihypertensive medicine, showing that generic substitution improved medication adherence, but a possible weakness of the study was a relatively short follow-up period of 180 days (25). Olesen et al. assessed adherence and generic substitution in an elderly population with polypharmacy by means of pill count, and the results of that study also showed that generic substitution did not affect adherence negatively (40). However, the indirect measure of adherence, that is pill count, has been found to overestimate adherence (95). Persistence studies often measure the duration of time from initiation to discontinuation of therapy in incident drugs users or previous "treatment naive" patients (35, 42, 96). Studies evaluating incident users of therapy may report lower estimates of persistence than our study, representing patients with at least two redemptions, since the largest non-persistence occurs within the first year of therapy (58).

What this study specifically shows is that first-time switching is the most critical point. Study I showed that experience with generic switching influences the acceptance of future generic switches positively. This study adds to the fact that experience with generic switching also has a positive influence on persistence.

In this study patients may redeem medicine packages with different numbers of tablets. Those with a small number of tablets are exposed to many medication changes during the 365 days of follow-up. A positive effect of this may be that the many medication changes bring extended information on generic substitution to the patient and may influence persistence positively. On the other hand, many generic switches may affect their persistence. During the one-year follow-up many things may happen and we do not know how many, how few, or if any generic switches take place, and whether this affects the patients' persistence behaviour. We have not taken this time-dependent variable into account in the model.

Concerns and cautions have been raised in relation to generic substitution of antidepressants and especially antiepileptics (20, 97). When looking at this study's two drug categories, the persistence estimate had the same direction with different results, but with overlapping confidence intervals. The non-

persistence estimate was higher among users of antiepileptics than among users of antidepressants. Generic substitution in the treatment of epilepsy has raised concerns at both patient and physician level. Despite the fact that anticonvulsants have a narrow therapeutic index, studies have shown that many physicians were likely to request brand antiepileptics “dispensed as written” because of concerns about breakthrough seizures (20, 98). Pechlivanoglou et al. showed that users of antidepressants were more prone to redeem brand-name products (91).

It is well known that decisions about taking medication are likely to be influenced by beliefs about medicines as well as beliefs about the illness, and studies have reported negative associations between low adherence and specific concerns about medicine (53, 99) and specifically for users of antiepileptics and antidepressants (100, 101). Results from the present study support these studies, showing that patients with a high level of concerns were negatively associated with persistence.

Surprisingly, negative views on generics were positively associated with persistence. A subsequent analysis was made to see if interaction was present among generic switches and views on generic medicine, however, no interaction was found. An explanation could be that patients having negative views on generics may have thought rationally about their medicine and over time chosen to take their medicine as prescribed. Study I showed that negative views on generic medicine were significantly more present among those who did not experience a generic switch of the index drug on the index day, and this may reduce the difference in non-persistence among generic switchers and non-switchers.

However, both questionnaire items did not affect our primary predictor considerably in the adjusted model.

6. CONCLUSION

Answers to the aim of the thesis:

Study I

In conclusion, the strongest positive association with making a generic switch was experience with generic switching within the index ATC code. Negative views towards generic medicine were negatively associated with making a generic switch. Patient characteristics like gender, age, number of different drugs used by the patients, and patients' confidence in the healthcare system and beliefs about medicine were not associated with making a generic switch.

Study II

The aim of the study was to investigate the possible association between patients' concern about their medicine and a specific generic switch. No additional concerns about medicine were found, when a generic switch on the index date took place, compared to those who did not switch.

Study III

The aim of the study was to examine how generic switching influences persistence to long-term treatment with focus on patients' concerns and views on generic medicine. The study found that patients who were first-time switchers of a specific drug were at higher risk of non-persistence compared to never switchers and those having experienced previous generic switching. Both concerns about medicine and negative views on generic medicine

were associated with a higher and a lower risk of non-persistence respectively. However, both variables did not considerably affect the primary predictor, i.e. generic switching, in the adjusted model.

7. IMPLICATIONS

Generic substitution has been implemented in practice for many years in Denmark. However, an evaluation is needed as generic substitution may have implications for the patients in terms of concerns and non-persistence.

The three studies could not identify a specific group of patients who were less willing to switch generics, nor became more concerned about their medicine after a generic switch had taken place. Negative views on generic medicines had a negative influence on the willingness to switch generic. A consistent theme in two of the studies was the importance of earlier experience with generic switching of a specific drug. Experience had a positive effect, both on the odds of making a generic switch and by having a protecting effect on non-persistence when using a generically substitutable drug, compared to those who experience their first generic switch.

There are undoubtedly other implications of generic substitutions that have not been investigated in the three studies. Future studies could include:

The cost-effectiveness of generic substitution. The implementation of generic substitution has resulted in substantial savings for the healthcare system, however, possible implications could occur. If patients do not take the medications as prescribed, this could result in more disease-related hospitalisations. Studies observing clinical outcomes and hospitalisations in correlation with generic substitution could be of relevance.

Socioeconomic factors' influence on generic substitution and the acceptance of generic switching. We could not identify a vulnerable group regarding generic switching and concerns after a generic switch when we looked at patient characteristics such as age and being treated with many different drugs. However, educational attainment and income may influence the willingness to make generic switches and persistence after generic switching has taken place.

Improvement of therapy treatment. Non-persistence constitutes a major barrier to control of chronic diseases, which may lead to morbidity and mortality (102). The present studies showed that experience with changes in medication due to generic substitution was of major importance for reducing the risk of non-persistence. Patients who experienced their first generic switch were most vulnerable to becoming non-persistent, indicating that they need special attention, e.g. information from prescribing physicians or pharmacy professionals. In order to reduce the risk of non-persistence it seems to be important to give words to potential changes that may undergo patients' medication, both at physician consultations and at the pharmacies. Generic prescribing has been discussed and a report has been completed, evaluating possible benefits or complications of generic prescribing across European countries (103). Generic prescribing is still not allowed in Denmark. However, focus on the name of the active substance could be of some relevance to patients, giving them a possibility of navigating by use of medication lists issued by physicians and by emphasizing the name of the active substance name

on a sticker on the drug package. The purpose of the sticker was to secure better recognition of the patients' medication and was introduced in Denmark in 2013.

Another consideration to take into account in order to facilitate patients' navigation between generically substitutable drugs is the consistency of the indication of the drug on the prescription every time a prescription is being renewed. Hence interventions should be developed targeting patients' first experience with generic switching and possibilities of navigating between generically substitutable drugs, to support physicians, pharmacists and most importantly patients in reducing the risk of non-persistence.

Generic substitution may imply a risk of therapeutic duplication. The magnitude of this potential problem has not yet been adequately addressed by research and the knowledge we have is primarily based on case reports (104). A qualitative study was conducted interviewing nurses about potential risk factors for medication errors in hospitals due to generic substitution (105). At present there are potential sources of errors when renewal of prescriptions takes place. It may be done by different GPs in the general practice or by one of the nurses or secretaries. In this process there may be renewed prescriptions on the same drug within a short period of time. The medication error may occur if the patient considers the drug, with different name or appearance, to be for different purposes and takes it simultaneously. At present there are no alarm warnings at GPs or at pharmacies, if the patients purchase the same drug with a different name within a short period of time.

Hence, there is a tremendous need for evaluation of possible duplication of purchased drugs. This evaluation should include quantitative research methods, including socioeconomic factors and possible clinical complications and hospitalisations due to drug duplication.

8. SUMMARY

Background:

Generic substitution means that one medicinal product is replaced by another product containing the same active substance. Generic substitution has existed in Denmark since 1991, and pharmacies are obliged to substitute a generic version of a medication, unless the general practitioner (GP) has explicitly stated that it should not be done, or the patient insists on having the more expensive drug. Generic prescribing, that is prescribing the substance name, is not allowed in Denmark.

Some specialists and patients cast doubt on the real interchangeability of generics, although international studies have shown that most patients have positive attitudes towards generic substitution. The severity of disease is known to be associated with patients being more concerned about generic substitution.

The generic substitution scheme implies changing from one drug to another that may vary in brand-name, form, size, colour and taste. Speculations have been raised as to whether these medication changes between generic brands or from brand-name drugs to generics or vice versa may cause patient concerns. Qualitative studies have shown problems in recognising the substituted medicine and lack of confidence in the identical effect of the substitutable medicines. Several studies have focused on one specific drug group such as antihypertensive drugs. However, the influence of generic switching may affect concerns about medi-

cine differently, depending on drug categories.

Research on generic substitution often focuses on incident drug users, whose prescription is substituted at their first redemption. Most of these studies did not identify significant associations between generic substitution and non-adherence, but one study assessing the association between generic substitution and persistence showed reduced persistence. So far, studies of the effect of generic drug substitution on drug continuation have not focused on patients' overall experience of generic switches within one specific drug.

Aims

To analyse associations between generic substitution and patient characteristics as well as patients' views on generic medicines, confidence in the healthcare system, beliefs about medicine, and experience with earlier generic substitution.

To investigate the possible association between a specific generic switch and patients' concerns about their medicine.

To examine how generic switch influences persistence with long-term treatment with special focus on importance of patients' concerns and views on generic medicine.

Methods

The design was a combined cross-sectional questionnaire and register study and additionally a cohort study. The study was conducted among 6000 medicine users, who had redeemed generically substitutable drugs with general reimbursement in September 2008 (2000 users of antidepressants, 2000 users of antiepileptics and 2000 users of other substitutable drugs), who were aged 20 years or older and living in the Region of Southern Denmark. The medicine users were identified through Odense PharmacoEpidemiologic Database (OPED). The purpose of the questionnaire survey was to elucidate patients' experience with medicine, combined with information from OPED on a single well-defined generic switch of the index drug. The questionnaire was adapted to the individual subject with reference to their specific drug (index drug) in every question and index date printed on the questionnaire.

The questionnaire comprises scales from the validated Beliefs about Medicine Questionnaire (BMQ) and ad hoc constructed scales. By means of OPED data it was possible to conduct a cohort study comprising information on all purchased medicine during the 12 months following the index date. The cohort comprised users of antidepressants and users of antiepileptics.

Results

A total of 2476 patients (44.1%) were included in the analyses. Experience with earlier generic switches within the index ATC code was associated with experience of a generic switch on the index day (OR 5.93; 95% CI 4.70–7.49). However, experience with earlier generic switches was drug-specific, e.g. having had more than five earlier switches within other ATC codes reduced the odds of experiencing a generic switch on the index day. Having negative views on generic medicines also reduced the odds of experiencing a generic switch on the index day.

Study II showed no statistically significant associations between experiencing a generic switch on the index day and having more or less concerns about the index medicine (-0.02 95% CI: -

0.10; 0.05).

Patients experiencing their first-time switch of a specific drug were at higher risk of non-persistence, Hazard Ratio 2.98, 95% CI (1.81;4.89), versus those who have never switched, and 35.7% became non-persistent during the first year of follow-up. Generic switching did not influence persistence considerably in those having previous experience with generic switching of the specific drug.

Conclusion

The overall results from the thesis showed that experience with earlier generic switches of a specific drug was associated with making a future generic switch and did not cause additional concerns about the index medicine. The effect of previous experience with generic substitution has been shown to be drug-specific. The third study showed that patients, who are first-time switchers of a specific drug, were at higher risk of becoming non-persistent compared to never switchers and those having experienced previous generic switching.

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