

Original Research

Evaluation of pharmaceutical concerns in Germany: frequency and potential reasons

Gabriele GRADL, Eva-Maria KRIEG, Martin SCHULZ 
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ABSTRACT*

Background: Generic substitution can have unintended consequences. In Germany, brand name to generic or generic to generic switching is mainly driven by rebate contracts. Frequent switching may raise concerns about bio- and therapeutic equivalence. Expected patient confusion may result in compromised medication adherence or new onset of other drug-related problems. Since 2008, pharmacists are allowed to deviate from rebate contracts by denying substitution due to pharmaceutical concerns on an individual basis.

Objectives: To explore the frequency of documented pharmaceutical concerns in Germany between July 2011 and December 2013 and to identify the medicines most frequently related to pharmaceutical concerns in 2013.

Methods: We analyzed documented pharmaceutical concerns in all prescribed drugs at the expense of any statutory health insurance company requiring pharmacies' generic substitution according to rebate contracts.

Results: Since July 2011, the frequency of documented pharmaceutical concerns in relation to prescribed drug products with rebate contracts requiring substitution increased consistently and doubled between July 2011 and July 2013. Overall in 2013, the trend of the two previous years continued and reached approximately 1.5%. The most affected drugs/drug classes were thyroid hormones (in particular combinations with iodide; 15.9%) followed by ondansetron (12.5%), and levothyroxine (11.3%). For all drugs/drug classes under investigation, product-, patient- or disease-related aspects could be identified which are potential reasons to deny substitution and to document pharmaceutical concerns.

Conclusions: Although there is no electronic recording of the specific reasons for pharmaceutical concerns in claims data, our analyses support the assumption that pharmacists make use of this instrument based on individual clinical decisions and as required by contract. Pharmaceutical concerns are, therefore, an important instrument for pharmacies to refuse generic substitution. They are considered to prevent compromised medication safety and to assure pharmacotherapy effectiveness in a generic substitution environment driven by low drug prizes above all.

Keywords: Drugs, Generic; Drug Substitution; Medication Adherence; Medication Errors; Patient Safety; Germany

INTRODUCTION

In the German healthcare system, 90% of the population is covered by the statutory health insurance (SHI) system organized in 118 competing insurance funds as of 1 January 2016. Within the German SHI system, the generic market (generic prescribing, and generic substitution) has become highly relevant in recent years¹⁻³ as around the world⁴⁻⁷, mainly in order to minimize costs.¹⁻³

Corresponding legislation in Germany initially allowed substitution with cheaper-priced drugs in the pharmacies only. Since 2007, it became mandatory for pharmacies to substitute the prescribed product for one where a rebate contract between the health insurance fund and a pharmaceutical manufacturer (Article 130a (8) Social Code Book V) has been negotiated (Gesetz zur Staerkung des Wettbewerbs in der Gesetzlichen Krankenversicherung (GKV-WSG 2007)). Rebate contracts are closed for any type of medicine requiring not only substituting an original by a generic. The contract may demand to exchange one generic by the other or even to exchange a prescribed generic for an original product.

As the prescriber is usually unaware of the details of the rebate contracts, the patient is confronted with substitution at the time of dispensing in the pharmacy for the very first time. Product substitution can, however, be prevented by the prescriber via ticking the 'aut idem' box on the prescription form, which was used in approximately 19% of prescriptions in 2008.^{8,9} If the 'aut idem' box is ticked, the pharmacist must dispense the prescribed product. In other words, if the 'aut idem' box is not ticked and a rebate contract between the statutory health insurance fund and a pharmaceutical manufacturer has been closed, the pharmacy is obliged to dispense this product irrespective of the prescribed one.

In 2008, the instrument of pharmaceutical concerns was introduced which allows pharmacies to deviate from rebate contracts denying substitution due to pharmaceutical concerns on an individual, case-by-case basis and if there are justified reasons to do so. This is the case, for example, when – in spite of additional counseling of the patient – therapeutic efficacy including medication adherence or drug safety is expected to be compromised. Reasons may be related to suspected non-adherence, handling or other drug-related problems if substituting i.e., dispensing the rebate contract product.^{10,11}

Besides the properties of the specific drug product such as active ingredient, dosage form,

* **Gabriele GRADL.** PhD. Research Associate, German Institute for Drug Use Evaluation (DAPI). Berlin (Germany). g.gradl@dapi.de

Eva-Maria KRIEG. RPh. Research Associate, German Institute for Drug Use Evaluation (DAPI). Berlin (Germany). e.krieg@dapi.de

Martin SCHULZ. PhD, FFIP, FESCP. Director Pharmacy, German Institute for Drug Use Evaluation (DAPI), Berlin; & Adjunct Professor Goethe-University Frankfurt; Lecturer, Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin. Berlin (Germany). m.schulz@dapi.de

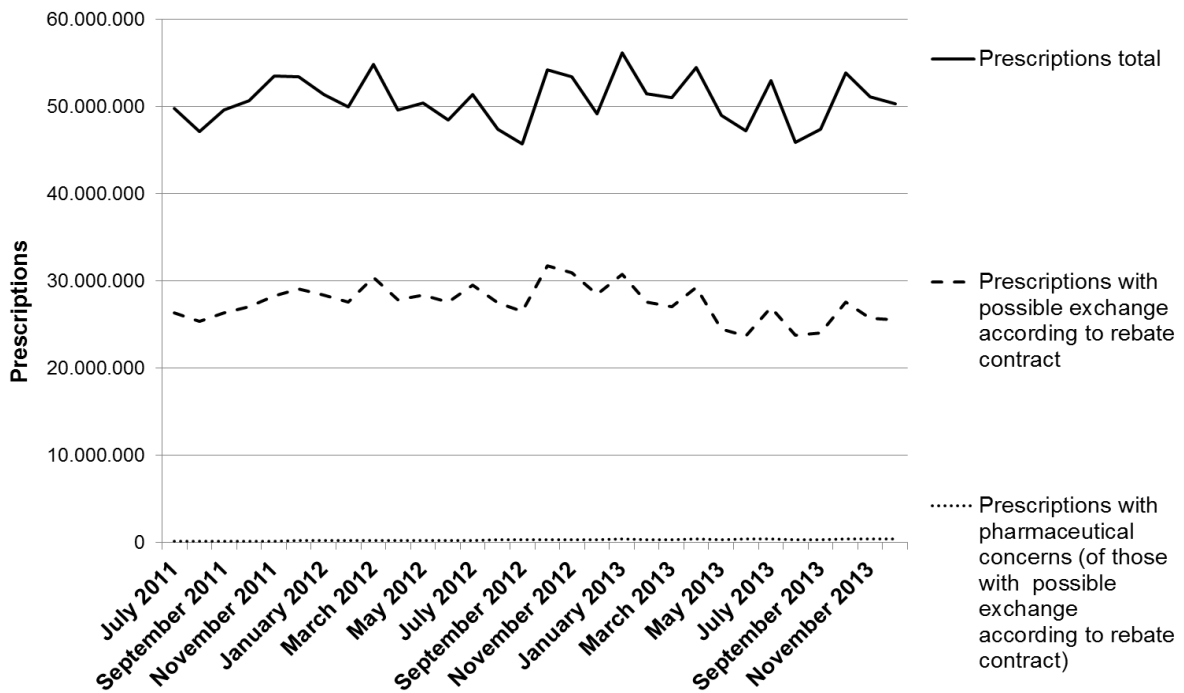


Figure 1. All prescriptions, prescriptions where exchange for a product under rebate contract would have been possible, and prescriptions with documented pharmaceutical concerns in Germany between July 2011 and December 2013.

handling/administration, or name/appearance, among others, the patient itself including type of disease, disease state/severity, or level of health literacy may influence the feasibility and acceptance of substitution. Hence, the decision to document pharmaceutical concerns is based on the pharmacist's professional judgment of the individual case. However, identifying frequent cases and finding out which drugs are most frequently concerned may be beneficial to identify common problems related to both rebate contracts and pharmaceutical concerns.

In a setting of being obliged to fill a prescription according to rebate contracts, the new instrument of documenting pharmaceutical concerns on a prescription and, thereby, to deviate from rebate contracts is an important tool for pharmacists to fulfill their duties in ensuring medication safety and quality of care. To the best of our knowledge, this instrument has not been studied before.

The aim of our study was to evaluate the frequency and potential reasons of pharmaceutical concerns.

METHODS

The database of the German Institute for Drug Use Evaluation (DAPI; www.dapi.de/en) comprises claims data of prescribed drugs dispensed at community pharmacies at the expense of SHI funds. This insurance system includes nearly 90% of the German population. The DAPI data cover claims data of more than 80% of all community pharmacies in Germany, without information on self-medication (over-the-counter drugs, OTC), dosing,

hospitalizations, diagnosis/indications or clinical data.

Prescription data are linked to the ABDA database containing a complete inventory of German medicinal products and other items which are dispensed by pharmacies. A linkage is possible via a specific product code ("Pharmazentralnummer" (PZN)). The PZN is a unique identifier for medicinal products that precisely defines each drug package and provides e.g., information about the (brand) name, composition, active ingredient(s), strength, dosage form, package size (including standard sizes N1, N2 or N3), and pharmaceutical company.

Since March 2011, technical documentation of pharmaceutical concerns and, hence, their quantification within pharmacy claims data were made possible by printing a specific code (2567024) on the prescription. This means that starting with this date it was possible to count prescriptions with documented pharmaceutical concerns. We continuously monitored documented pharmaceutical concerns for medicines dispensed at community pharmacies in Germany at the expense of the statutory health insurance funds, starting in July 2011, by determining the frequency and type of products concerned utilizing the ATC code. We considered items prescribed only if the 'aut idem' box on the prescription was not ticked by the prescriber and generic substitution was possible and required by closed rebate contracts for this item by the specific SHI fund and a pharmaceutical manufacturer. These criteria were true for approximately 53% of the 611 million prescriptions

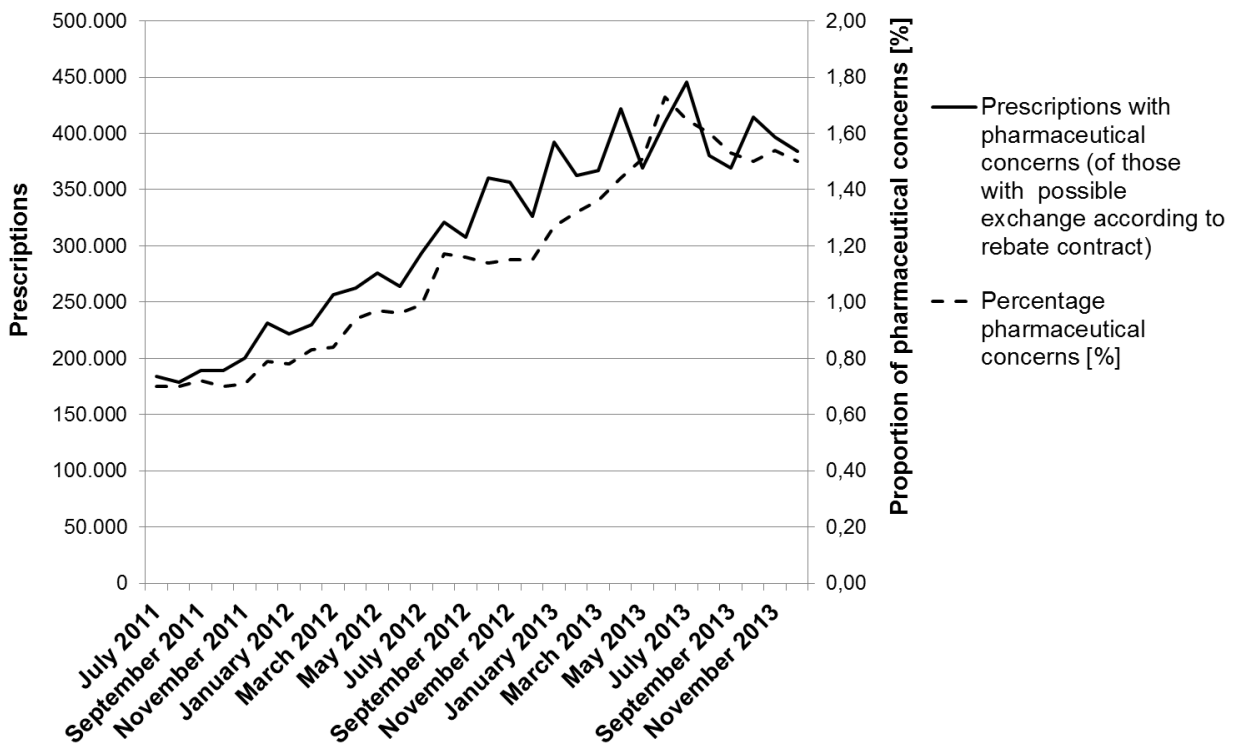


Figure 2. Prescriptions with documented pharmaceutical concerns (left y-axis) and proportion of prescriptions with documented pharmaceutical concerns of those prescriptions where exchange for a product under rebate contract would have been possible (right y-axis) in Germany between July 2011 and December 2013.

of medicines to the expense of SHI funds in German community pharmacies in 2013.

RESULTS

The overall number of documented pharmaceutical concerns is, related to the number of all prescriptions, very low, as can be seen in Figure 1. During 2011, there was no notable increase in the proportion of pharmaceutical concerns in relation to those prescriptions which were eligible for substitution due to at least one existing rebate contract and with the 'aut idem' box on the prescription not ticked. This situation changed in 2012 when the frequency of documented pharmaceutical concerns in relation to prescribed items with rebate contracts requiring substitution increased consistently and doubled until July 2013. Overall in 2013, the trend of 2012 continued and reached approximately 1.5% (Figure 2).

Figure 3 shows the 20 drug substances most frequently related to pharmaceutical concerns in 2013. Top drugs/drug classes (>10%) were thyroid hormones (in particular combinations with iodide; ATC code H03AA, 15.9% of 1.44 million prescriptions), ondansetron (A04AA01, 12.5% of 0.14 million prescriptions), levothyroxine (H03AA01, 11.3% of 8.45 Mio. prescriptions), phenprocoumon (B01AA04, 11.0% of 2.00 Mio. prescriptions), and estradiol (G03CA03, 10.4% of 0.12 million prescriptions).

DISCUSSION

Pharmaceutical concerns are an important instrument for pharmacists to refuse generic substitution required by law and closed rebate contracts between health insurance funds and pharmaceutical companies. Since July 2011, the frequency of documented pharmaceutical concerns in relation to prescribed drug products with rebate contracts requiring substitution increased consistently and doubled between July 2011 and July 2013. Overall in 2013, the trend of the two previous years continued and reached approximately 1.5%.

When a pharmacist documents pharmaceutical concerns on a prescription, he is obliged to note the reason on the prescription form. These handwritten notes are not available electronically. Reasons for pharmaceutical concerns are diverse.^{1,10,12} They may result from circumstances of an individual person prescribed a concrete medicine. Hence, analyzing claims data does not allow exploration of individual reasons for pharmaceutical concerns documented. However, looking at the medicines frequently related to pharmaceutical concerns in detail, we found drugs with a narrow therapeutic index or a high potential for side effects (critical-dose drugs), dosage forms difficult to handle or administer by the patient and/or care giver, or medicines for severe, psychiatric or neurological diseases.

First, we identified drugs with a narrow therapeutic index or variable bioavailability requiring dose

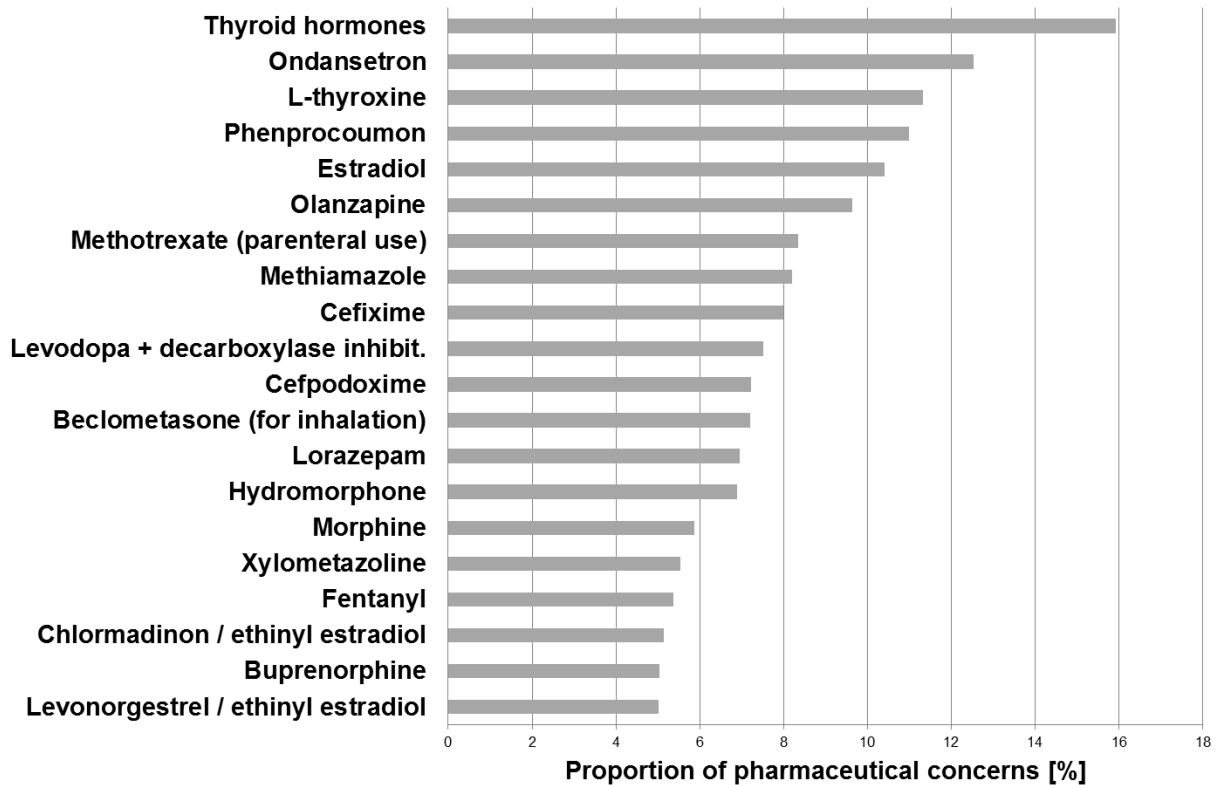


Figure 3. Drug substances most frequently related to pharmaceutical concerns in 2013. Percentages of prescribed items requiring substitution according to rebate contracts [detailed information is provided in online appendix Figures a to e].

individualization such as thyroid hormones (levothyroxine, among others), the vitamin-K antagonist (VKA) phenprocoumon (used instead of warfarin in Germany), the thyreostatic thiamazole (see Figure 3 and online appendix Figure a), and levodopa. Especially VKAs bear the risk of thromboembolic events or increased bleeding risk when deviating from the individually defined dose.^{1,11,13,14} Even small dose changes of thyroid hormones such as levothyroxine may result in signs of clinical hyper- or hypothyreosis.¹⁵ Consequently, nearly all Summaries of Product Characteristics (SPC) of levothyroxine products require close monitoring including laboratory controls (TSH, fT4) when substituting.

These aspects, among others, resulted in the decision of the Federal Joint Committee (Gemeinsame Bundesausschuss (G-BA)) as of 18 September 2014 to include levothyroxine-sodium in tablets (both as mono therapy and as fixed-dosed combination containing potassium iodide) to the first list of medicines excluded from generic substitution.¹⁶ According to Article 129 (1a) sentence 2 Social Code Book V, the Federal Joint Committee is entitled to exclude specific drugs, especially those with a narrow therapeutic index, from substitution.

Secondly, pharmaceutical concerns were documented for specific dosage forms (see Figure 3 and online appendix Figures b, and c): transdermal therapeutic systems (TTS; patches containing e.g. estradiol, fentanyl, buprenorphine), sustained-/modified released dosage forms (e.g. opioids such as hydromorphone and morphine), parenteral

dosage forms of high-risk substances (e.g. methotrexate) as well as inhalers (e.g. inhaled corticosteroids such as beclometasone). Since (metered-dose- or dry-powder-) inhalers are difficult to handle in general and inhalation technique is poor^{17,18}, pharmaceutical concerns may (and shall) be used to prevent drug-related problems in asthma or COPD patients due to (frequent) generic substitution.¹⁹

Further specific dosage forms frequently related to pharmaceutical concerns are orodispersible tablets containing, for example, the benzodiazepine lorazepam or the antiemetic ondansetron. In these cases, rebate contracts of two large health insurance funds, the local health insurance funds AOK (35% market share in 2013) and BARMER GEK, a substitutional social health insurance fund (13% market share in 2013), included coated tablets only. Substituting orodispersible tablets in patients with difficulties to swallow larger dosage forms or if a more rapid effect is required may cause problems. However, orodispersible dosage forms are not always the first choice as, among other reasons, these are usually moisture-sensitive and coated tablets are more stable if dispensed in weekly dosing-aids (dosettes).

Another reason for pharmaceutical concerns can be related to different package sizes between the prescribed product and the product to be dispensed according to the rebate contract. This problem is probably the cause for pharmaceutical concerns documented on prescriptions for the cephalosporin antibiotics cefixime and cefpodoxime. For cefixime for example, these were mostly documented if the

specific rebate contract required dispensing the standard package size N1 (smallest available on the market) containing five tablets whereas the dispensed, and probably prescribed, N1-product contained seven tablets.

Apart from the specific medicine, the disease itself and resultant circumstances may be a reason to avoid substitution and to eventually document pharmaceutical concerns.¹⁰ This is imaginable in severe disease states when patients' or care givers' familiarity with the used medicine should not be compromised by substitution. This holds true e.g., for potent analgesics such as opioids (hydromorphone) and opiates (morphine) or in the case of neurological (antiepileptics²⁰ or levodopa) or psychiatric illnesses (for example, the antipsychotic olanzapine).

Concerns about compromised medication adherence may be another reason for pharmacists to document pharmaceutical concerns, for example when changes in the appearance of drug packages from one product to another can confuse the patient. Given the low medication adherence to long-term therapies (on average 50%, only)²¹, one would expect that the frequency of documented pharmaceutical concerns assuming a compromised medication adherence by dispensing a rebate product unknown to the patient should be much higher.²²⁻²⁵ However, the extent of this effect is not quantifiable as the literature on the impact of generic substitution on medication adherence is scarce. Changing from the ramipril originator to a generic did not significantly affect pharmacy refill compliance²⁶ and changing from a brand-name atorvastatin to a generic product did not affect adherence of patients newly treated with atorvastatin.²⁷ Hence, assuming compromised medication adherence when preventing generic substitution is not universally accepted as appropriate pharmaceutical concern. One example where a lack of medication adherence is assumed when changing between brands are oral contraceptives, which may be prescribed at the expense of the SHI funds for women younger than 20 years.¹²

In summary and given the wide-spread problem of medication non-adherence^{21,22,28-30}, the overall relatively low number of documented

pharmaceutical concerns across Germany does not give reason to assume that pharmacists overuse this instrument, so far.

We are not aware of significant changes in guidelines relevant to generic substitution during the analyzed periods. In addition, changes in the guidelines for German pharmacists in making use of the instrument of pharmaceutical concerns were not published. Therefore, we conclude that the changes in the proportion of pharmaceutical concerns for the various drugs, as depicted in online appendix Figures a) to e), are mainly driven by changes in rebate contracts.

We abstained analyzing the economic impact of documented pharmaceutical concerns since key data for this analysis are not available: rebate prices are not disclosed to the public. The overall number of prescriptions with documented pharmaceutical concerns is very low and many prescriptions are not eligible to dispense a rebate instead of the prescribed product. Hence, the potential budget impact of pharmaceutical concerns can be neglected.

CONCLUSIONS

Pharmaceutical concerns are an important instrument for pharmacies to refuse generic substitution required by law and closed rebate contracts between health insurance funds and pharmaceutical companies. Although analyzing claims data does not allow exploration of the specific reasons for pharmaceutical concerns, our analyses of the data support the assumption that pharmacists make use of this instrument based on individual clinical decisions and as required by contract. Pharmaceutical concerns are considered to prevent compromised medication adherence and safety assuring pharmacotherapy effectiveness in a generic substitution environment driven by low drug prizes above all.

CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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