

Over-the-counter (OTC) drug regulation and the epidemiology of OTC drug use in Germany

Dissertation

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Danksagung

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List of abbreviations

ADR	adverse drug reaction
AMG	German Medicinal Products Act [Arzneimittelgesetz]
BfArM	German Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte]
BGS98	German Federal Health Survey of 1998 [Bundesgesundheitsurvey]
DEGS1	first phase of the German Health Interview and Examination Survey for Adults [Studie zur Gesundheit Erwachsener in Deutschland]
EAC	Expert Advisory Committee for Prescription-Only Issues
EU	European Union
FDA	Food and Drug Administration
G-BA	Federal Joint Committee [Gemeinsamer Bundesausschuss]
NRW	North-Rhine Westphalia
OTC	over-the-counter
PZN	German identification number for pharmaceutical products [Pharmazentralnummer]
RKI	Robert Koch-Institut
Rx	prescription-only
SHI	statutory health insurance
SPC	summary of product characteristics
USA	United States of America
WHO	World Health Organization

Preface

The present thesis is based on four original research articles that are listed below. The following text seeks to summarize the findings, to highlight their respective interlinkages and to integrate and discuss them in a broader public health context.

- Barrenberg E, Garbe E (2015) Use of over-the-counter (OTC) drugs and perceptions of OTC drug safety among German adults. *European Journal of Clinical Pharmacology*, 71(11):1389–1396. doi: 10.1007/s00228-015-1929-5.
- Barrenberg E, Garbe E (2017) Unsuccessful applications to increase or decrease the over-the-counter (OTC) availability of drugs in Germany between 2009 and 2014. *Journal of Public Health*, 25(3):321-331. doi:10.1007/s10389-016-0782-z.
- Barrenberg E, Garbe E (2017) From prescription-only (Rx) to over-the-counter (OTC) status in Germany 2006–2015: pharmacological perspectives on regulatory decisions. *European Journal of Clinical Pharmacology*, 73(7):901-910. doi: 10.1007/s00228-017-2240-4.
- Barrenberg E, Knopf H, Garbe E (2018) Over-the-counter drug consumption among adults living in Germany: Results from the German Health Interview and Examination Survey for Adults 2008–2011 (DEGS1). *Pharmacy* 2018, 6(2), 52. Special Issue: The Standing of OTC Medicines in Community Practice. doi:10.3390/pharmacy6020052

1. Introduction

Next to health promotion, health protection and health services research are integral and traditional subjects of the public health discipline. Public health research and practice concern themselves with the careful balancing of different public interests and considerations to achieve the greatest possible and equitable population health outcomes. For example, public health practice must ensure efficient access to effective and safe pharmaceuticals, while protecting the population from health risks related to the inappropriate use of pharmaceuticals.

The present thesis addresses several public health dimensions of over-the-counter (OTC) drugs in Germany, such as the prevalence of OTC drug use, societal risk perceptions, regulatory decisions and pharmacological perspectives. It provides a chapter outlining background information, followed by three chapters based on the original research articles underlying the thesis, covering OTC drug use, changes to drug trade statuses and perceptions of OTC drug safety in Germany. Finally, the overall findings are discussed in the light of public health theory and practice before concluding remarks are made. Authorized reprints of the original research articles and their supplementary materials are presented in the annexes.

2. Background

OTC drug use and its regulation are topics that reflect the common trade-offs of the public health discipline: benefits from OTC drug availability should be maximized on the one hand and potential harm from OTC drugs should be minimized on the other hand. OTC drugs help to enhance patient empowerment by giving patients the opportunity to treat minor illnesses themselves and to decide whether a condition requires treatment with medication at all (1). These considerations are countered by the task of public health to provide adequate health protection. That is, if a medication is being admitted to the market as an OTC drug, it must be safe to the extent that it can be sold without prescription, which goes beyond general requirements for drug safety (1). As this is an area that is solely the task of public authorities and cannot be taken care of by individuals, ensuring OTC drug safety is a public health task per se.

Furthermore, OTC availability of drugs links to the increased pressure to save costs in public health care arrangements (2). The increased OTC availability of drugs saves general practitioners' time and increases convenience for patients, proves a higher valorization of pharmacists' expertise and decreases the spending of health insurers. However, OTC drug use also carries the risk of wrong self-diagnoses, which may result in the consumption of inappropriate medicines and late presentation to formal health services (3).

2.1 Drug trade statuses in Germany

In Germany, a distinction is made between four different trade statuses of drugs: (i) prescription drugs that fall under the Narcotics Control Act [Betäubungsmittelgesetz], (ii) prescription drugs that can be administered within health care settings or obtained in a pharmacy, (iii) OTC drugs that can be obtained in pharmacies only and (iv) OTC drugs that can be bought in pharmacies or any other retail facility. Drugs can be 'switched' from one trade status category into another. Throughout this thesis, OTC drugs will refer to the third category and 'switches' will refer to reclassifications between the second and third categories, unless otherwise indicated.

The German Medicinal Products Act [Arzneimittelgesetz] (AMG) (4) stipulates that new substances or combinations of substances for which no pharmacovigilance data exist should be available as prescription-only (Rx) drugs. Also, active ingredients or combinations of active ingredients that can directly or indirectly harm human health, the health of the user or the environment, when used in line with the instructions but without a medical prescription, should also be available only as Rx drugs. Moreover, substances that are used not according to their intended purposes with significant frequency, and can thereby cause direct or indirect harm to human health, should be available only as Rx drugs (4). The German legal framework does not set out explicitly which substances can become OTC drugs, as OTC status is, in legal terms, considered the 'default' trade status. It is the Ministry of Health, in agreement with the Ministry of Economics and Technology, conditional on the approval of the Bundesrat (Council of the Federal States), that specifies those substances whose use requires medical supervision and which should thus be available only as Rx drugs. All Rx substances for human and veterinary use are listed in annex 1 of the Ordinance on Prescription-Only Medicines [Arzneimittelverschreibungsverordnung] (5). Changes to the Ordinance require approval by the Bundesrat and signatures of the relevant ministers (4).

The AMG also specifies that Rx status has to be lifted once enough information is available to ensure that a drug can be used safely without medical supervision (§ 48 II 1 Nr. 3 AMG). For new substances, three years after initial market launch is the earliest time switch applications can be made (§ 48 II 1 Nr. 3 AMG). The lifting of Rx status can be limited to certain dosages, potentiations, pharmaceutical forms, finished medicinal products or applications. Also, OTC availability can be limited to midwives who would need a drug for the proper practice of their profession (4).

Moreover, the AMG states that changes in the prescription status of medicines require prior consultation with experts (§ 48 II 2 AMG) (4). The Expert Advisory Committee for Prescription-Only Issues (EAC) [Sachverständigen-Ausschuss für Verschreibungspflicht] deals with questions of Rx and OTC status, in particular. The EAC consists of nine professors, covering the areas of clinical pharmacology, clinical pharmacy, internal medicine, general practice, paediatrics, veterinary medicine and epidemiology or statistics. The EAC also comprises three representatives of the expert drug committees of the German Medical Association [Arzneimittelkommission der deutschen Ärzteschaft], the German Chamber of Veterinarians [Arzneimittelkommission der Tierärzte] and the umbrella organization of German pharmacists' professional associations [Arzneimittelkommission der Deutschen Apotheker]. EAC members without the right to vote include three medical practitioners from different specialisms (general practice, internal medicine and paediatrics), a dentist, a veterinarian, a naturopath, a pharmacists' representative, two representatives of the pharmaceutical industry of human medicines and one representative of the pharmaceutical industry of veterinary medicines. The experts serve voluntarily and are nominated for a five-year term. They have the right to submit a written resignation from the EAC at any time, and have to maintain confidentiality about the items discussed. The German Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte] (BfArM) serves the EAC as a secretariat and provides scientific support (6).

The current terms and conditions for the EAC date from 2016 (7) and were preceded by the terms and conditions for expert advisory committees for standardized marketing authorization, Rx issues and pharmacy-only issues, which were originally put in place in 1978 (8). They specify that the BfArM has to prepare a statement providing a foundation for the medical and pharmaceutical aspects of EAC decisions. The terms and conditions also make provisions for possible conflicts of interest and stipulate that the chair of the EAC can invite external experts to be heard, provided the committee members give their consent (7).

2.2 Changes to drug trade statuses in Germany

Any legal (e.g. a company or an organisation) or natural (a human being) person can submit an application for a change in a drug's trade status to the BfArM. On its website, the BfArM informs potential applicants of the materials required for such a submission. These include:

- a statement regarding the prescription status and, if the application does not refer to a general Rx-to-OTC or OTC-to-Rx switch for the substance in question, precise wording on what type of exception is applied for – exceptions can relate to pharmaceutical form, indication, maximum single and/or daily dose and pack size;
- the latest versions of the health-care provider's information (summary of product characteristics (SPC)) and package leaflet, and the date of the substance's market launch;
- sales/distribution figures and an estimated number of treated patients, including the method of calculation: the BfArM encourages applicants to include a list with distribution figures from countries where the substance in question is already available under the trade status the applicant seeks to request (e.g. in the context of an Rx-to-OTC switch application, data from a country where the medicine is already available OTC should be submitted);
- documents such as scientific publications and expert reports supporting the argumentation of the submitted application.

In the context of the last requirement, the BfArM emphasizes that recommendations made by the EAC are, above all, based on verifiable evidence regarding risks associated with the medicine under consideration (9). The BfArM has two annual deadlines for accepting applications for changes in prescription status. Accordingly, EAC meetings are usually held twice a year (10). The process and stakeholders involved in changes to drugs' trade status is summarized in Figure 1.

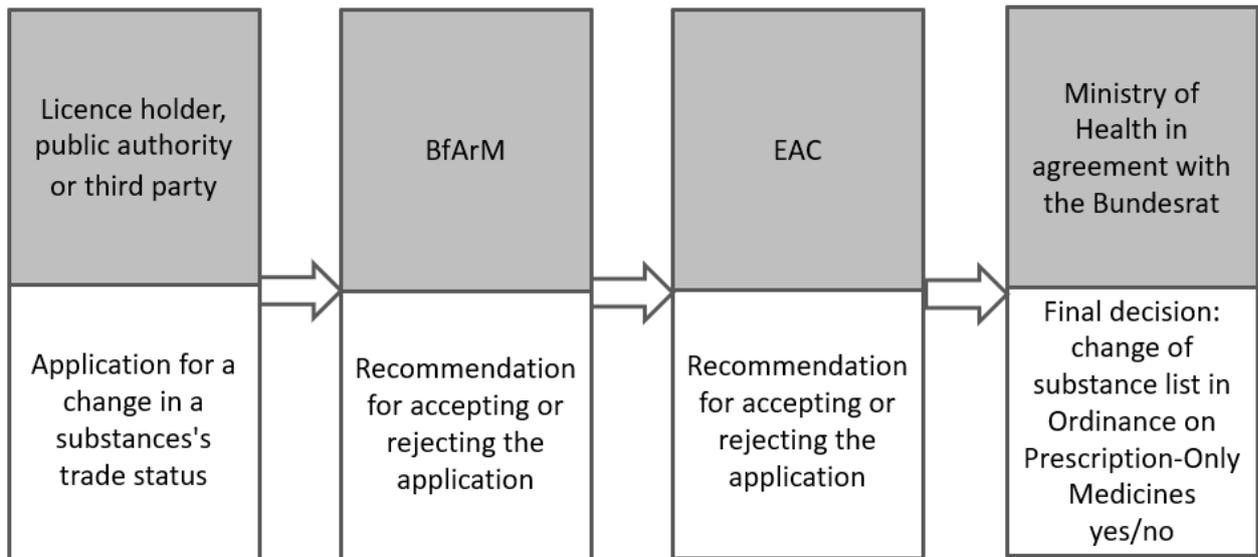


Figure 1: Process of changes to drugs' trade status in Germany

A particular feature of the German legal framework for changes to drugs' trade statuses is that they are substance-based, whereas some other European Union (EU) countries make product-specific decisions on trade status (11). In Germany, legal changes on trade statuses therefore apply to all products with the same active ingredient(s) at the same given dose, pack size, pharmaceutical form, indication and other possible restrictions. For example, in 2009 it was decided to grant OTC status to omeprazole for treatment of symptoms such as heartburn and acid regurgitation which require a sustainable reduction of gastric acid production, in a single and a maximum daily dose of 20 mg, with a therapy duration limited to a maximum of 14 days, and in a maximum pack size of 280 mg of the active substance (12). This decision thus applies to all omeprazole products with these features, across all brands marketed in Germany. However, omeprazole products with a different indication – e.g. for the treatment of gastric ulcers – remain Rx drugs (13). Thus, legally speaking, a substance with a specific set of restrictions can only either have Rx or OTC status and it is not possible to market the same product under both trade statuses at the same time. Nevertheless, from a clinical perspective, it can be argued that there are a few drugs which are available with OTC and Rx status in parallel.

2.3 OTC drugs in the context of the German health care system

The majority of the German population (85%) is covered by statutory health insurance (SHI), while 11% of Germans are enrolled in private health insurance and 4% are covered through specific governmental schemes (e.g. the scheme for members of the military). Since a health reform in 2009, some type of health insurance is mandatory for all citizens (14). Patients have a free choice of SHI funds and of the pharmacies, generalist and specialist physicians in the ambulatory care sector and hospitals they visit. They also have direct access to secondary care (14, 15). The German public health care system is based on the principle of self-governance with the Federal Joint Committee [Gemeinsamer Bundesausschuss] (G-BA) as its highest decision-making body. The G-BA includes representatives from SHI funds and providers of care, as well as patient representatives. The latter do not have voting rights (14, 16).

In order to reduce pharmaceutical spending, the SHI Modernization Act [GKV-Modernisierungsgesetz] states that, as of 2004, OTC drugs are no longer reimbursable by SHI funds (17, 18). Exceptions apply to children aged below twelve years and children with developmental disorders aged below 18 years. For these groups, OTC drugs can still be prescribed and fully reimbursed (19). Another exception is a list of around 45 OTC substances which remain reimbursable upon prescription in cases of severe and/or chronic diseases (19, 20). Pharmaceutical companies can make applications to the G-BA for their OTC drugs to be included on that list (18). Since 2012, reimbursement for some OTC drugs can be offered as an *ex gratia* payment by certain SHI funds, for which a prescription by a physician is usually a prerequisite (21, 22).

The decision to stop reimbursement of OTC drugs was considered socially acceptable due to the average price of eleven euros per pack of OTC drugs and because OTC drugs had already been predominantly dispensed without prescriptions (18). The SHI Modernization Act also permitted online pharmacies and liberalized the prices of OTC drugs, with the expectation of lower prices through competition. However, in studies made between 2007 and 2014, no overall decrease in OTC drug prices has been observed, although there have been changes in pricing patterns, including those resulting from online trade (14, 23, 24). Rx drugs are generally eligible for reimbursement by SHI funds and are subject to a variety of regulations for the purpose of cost-containment, including provisions on comparative cost-effectiveness assessments (14, 25, 26). In most cases, patients are required to effect a co-payment of five to ten euros, although exceptions exist for drugs with specific pricing schemes and patients with low incomes and chronic diseases (14, 25). Alongside OTC drugs, the SHI Modernization Act excluded lifestyle drugs from reimbursement. The Act and the G-BA

identified the following categories of lifestyle drugs: products to aid weight loss, to aid smoking cessation, to increase sexual desire, to improve the outward appearance, to treat sexual dysfunction and to treat hair loss (22, 27). Moreover, the G-BA can exclude drugs from reimbursement on the basis of proven inappropriateness or if cheaper drugs with similar diagnostic or therapeutic uses are available (28).

Patients can buy OTC drugs in pharmacies at their own discretion and without prior consultation of a physician. For privately insured patients, physicians can also prescribe OTC drugs, which are generally reimbursed by their health insurance companies. For publicly insured patients, physicians can recommend OTC drugs using a so-called 'green prescription form' [Grünes Rezept] (17). As with Rx drugs, pharmacies are obliged to provide information and advice on OTC drugs, in particular about their safe use, correct storage and disposal, adverse effects and interactions, whether the desired drug is adequate for the person intending to use it and whether a physician should be consulted. They must also ask whether the patient or other client has any further questions (29, 30). With the entry into force of the SHI Modernization Act in 2004, mail order for drugs is also permitted, on the condition that mail-order pharmacies comply with all the provisions that are legally required in brick-and-mortar pharmacies (22, 31).

2.4 The interface of national and EU regulations on drug trade statuses

The EU Directive on medicinal products for human use (2001/83/EC) (32) is more explicit on prescription and non-prescription medicines than German national legislation. It is suggested that OTC status should not be granted to drugs if they (i) "are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or (ii) are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or (iii) contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or (iv) are normally prescribed by a doctor to be administered parenterally". The Directive also states that OTC status should be excluded if a "medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971", or (v) "is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes". Additional considerations pertaining to Rx status are if drugs are (vi) "reserved for treatments which can only be followed in a hospital environment", are (vii) "used in the treatment of conditions which

must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere” or are (viii) “intended for outpatients but” their “use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment” (32).

Moreover, different types of EU market authorization procedures for pharmaceuticals can have an impact on changes of trade status at the national level. Pharmaceuticals can be authorized by national authorities for the domestic market. Alongside this purely national procedure, three European procedures can be distinguished (33-35). In the ‘mutual-recognition procedure’, marketing authorization is granted through mutual recognition by one or more Member States that a product has already been approved by the authorities of another – the reference Member State. The ‘decentralised procedure’ is similar in terms of mutual recognition and the role of a reference Member State, except that it is used for products which do not yet have market authorization in any EU country at the time the decentralised procedure is used. The reference Member State also approves the SPC, the labelling and the package leaflet. The mutual recognition procedure and the decentralised procedure imply that different national markets can only be accessed one by one (33, 34). In contrast, the ‘centralised procedure’ offers access to all national markets of the EU simultaneously (33). It “is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, ... orphan medicinal products and any medicinal product for human use containing an entirely new active substance, i.e. one that has not yet been authorised in the Community, and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes” (36). The centralised procedure is “optional for medicinal products which ... are ... therapeutically innovative” or “although not innovative, may be of benefit to society or to patients if they are authorised from the outset at Community level, such as certain medicinal products which can be supplied without a medical prescription” (36).

As regards applications for changes in drug trade statuses, these can also be made at the EU level through the centralised procedure, which uses a product-based approach. It was outside the scope of this thesis to analyse comprehensively which products gained OTC status through the European centralised procedure. Nonetheless, prominent examples in recent years have included the first centralised switch of orlistat, a weight-loss medicine; pantoprazole, a proton-pump inhibitor to treat gastro-oesophageal reflux disease; and tamsulosin hydrochloride to treat benign prostate hyperplasia in 2009 (37), as well as esomeprazole to treat gastro-oesophageal reflux disease in 2014 (38) and ulipristal acetate as a product for emergency contraception in 2015 (39). However, according to the views of the Association of the European Self-Medication Industry and the head of

the German Medicines Manufacturers' Association, licence holders are reluctant to choose the centralised switch procedure, because in the case of a negative decision licence holders are precluded from submitting applications for Rx-to-OTC switches in individual Member States (40, 41).

As set out in § 48 II 2 of the AMG, the EAC cannot provide recommendations either on the trade status of products admitted to the EU market through the centralised procedure or on equivalent drugs in terms of active ingredient, indication, dose and pharmaceutical form. However, the Ministry of Health intends to inform the EAC about changes that are expected to occur in the Ordinance on Prescription-Only Medicines through the centralised procedure and may consult the EAC on questions of wording (42, 43). The Ministry has also offered to consult the EAC experts regarding the question of whether a centrally induced product-based switch should translate into a substance-based switch at the national level, in cases where nationally admitted products with the same active ingredient exist (42).

The interwoven relationship of European and national procedures for market admission and changes to prescription status has a number of implications for the EAC's work. For example, when advising on applications for changes in prescription status of drugs that have been admitted to the market through the European decentralised procedure or the mutual recognition procedure, the EAC should not make its recommendations conditional upon changes to the sections on contraindications or warnings in the package leaflet. This is because changes to the sections on contraindications and warnings in the package leaflets of such drugs cannot be made at the national level, even if the decision to change that drug's prescription status is being made at the national level. Such recommendations are also to be avoided in national switch applications regarding nationally admitted substances, due to the possibility that a product with the same active ingredient could be switched through the centralised procedure at a later point in time, which would then result in conflicting German and European stipulations (42, 44-47). Instead, possible risk-reducing measures for drugs being switched from Rx to OTC status available to the EAC include the following: restriction of licensed indications; specification of pharmaceutical form, restriction of dose or potentiation, patient population or duration of use; and restriction of pack size (47).

Another field where EU legislation interacts with national switch decisions is direct-to-consumer advertising. According to EU Directive 2001/83/EC, direct-to-consumer advertising is prohibited for Rx drugs but allowed for OTC drugs. In addition, the Directive sets out various rules for advertising and specifies that Member States can prohibit advertisement of products that can be reimbursed by the public health care system (32). Member States can make exceptions to the permission to advertise OTC drugs directly to consumers, but as the German Health Services and Products Advertising Act [Heilmittelwerbegesetz] needs to be closely aligned with the pertinent EU Directive,

such exceptions can be legally challenging (32, 48, 49). A recent example of such an exception was the direct-to-consumer advertising ban of products for emergency contraception after their Rx-to-OTC switch had been approved in 2015 (50). The direct-to-consumer advertising ban for products for emergency contraception is in line with a previous suggestion of an EAC member, but this was not a direct cause of its implementation, since proposing changes to the Health Services and Products Advertising Act is generally outside the mandate of the EAC (49, 51).

Furthermore, according to article 74a of EU Directive 2001/83/EC, a period of market exclusivity of one year can be granted to licence holders after a change of trade status that “has been authorised on the basis of significant pre-clinical tests or clinical trials” (32). That is, for example, if a licence holder makes significant investments in further research in order to prove the suitability for OTC status of its products, it can request to market its product exclusively under the new trade status before the same status can be granted to other products with the same active ingredient (32, 37). This provision on market exclusivity has also been transposed into German law (4). So far, market exclusivity has never been granted in the context of national switch decisions in Germany. Only on the occasion of the centralised switch decision of ulipristal acetate, market exclusivity was granted to the licence holder at the EU level. After transposing the centralised switch decision into German law, the brand name was reflected in the annex of the Ordinance on Prescription-Only Medicines for the first year (52).

2.5 Rx-to-OTC switch criteria

While pharmaceuticals are considered to be among the best regulated consumer products, there is little ‘hard’ normative guidance regarding the transition between Rx status and OTC status. At the national level in Germany, written information is limited to reflections shared by a BfArM officer during the inaugural session of the newly constituted EAC in 2013. She drew attention to the following points for consideration during deliberations on Rx-to-OTC or OTC-to-Rx switch applications. Risks in the context of self-medication should be evaluated in the light of adverse drug reactions (ADRs) during appropriate use (including the type and severity of ADR) and potential for abuse, while considering existing pharmacovigilance and research data, including the respective quantity and quality of such data. ADRs should also be considered in the light of special risk groups, such as children, pregnant women, elderly people and patients with organ disorders. Moreover, the EAC should consider the therapeutic index, including whether unintentional overdosing is possible – e.g. due to a lack of effectiveness – and whether there is a risk of inappropriate use by children,

accumulation or possible fatal outcomes. In addition, the EAC might wish to consider the questions of whether a change in trade status should be applied to all approved indications; whether the indications are suitable for self-diagnosis; whether there is a risk of misdiagnosis and, if so, which consequences could result from misdiagnosis; and whether the drug is intended for parenteral application (53). In 1985, the then president of the German Federal Pharmacy Chamber [Bundesapothekerkammer] demanded that pharmacists should be allowed to sell Rx drugs without a prescription for 1–3 uses in acute cases. He formulated pharmacological criteria that should be fulfilled for possible drugs in question, referring to an earlier report of the expert drug committee of the umbrella organization of German pharmacists' professional associations. The criteria were that the drug should: be effective at the relevant dose, have a large therapeutic index, have hardly any adverse effects at the designated dose, have no addictive properties, be pharmacologically well studied and not delay consultation of a physician or mask symptoms (54).

At EU level, normative guidance is limited to the Guideline on changing the classification for the supply of a medicinal product for human use (the 'EU switch guide') (55). Next to the issue of market exclusivity and data requirements, the EU switch guide deals with criteria for classifying a drug as having Rx or OTC status and how to determine these criteria. For example, it mentions that OTC drugs should have "low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties" as well as a "low risk of serious type A adverse reactions in the general population", a "very low risk of serious type B reactions" and "no interactions with commonly used medicines which can produce serious adverse reactions". At the same time, the EU switch guide mentions that these criteria should be put into the perspective of possible preventive action: "for example, serious type A reactions can be acceptable if there is a clear identifiable risk group that can be excluded even in the absence of medical supervision", and that the risk of a product should be considered relative to the risk of an alternative treatment. Furthermore, it mentions the risk of OTC drugs masking more severe underlying conditions and the related link to delaying diagnosis thereof. The EU switch guide expands on the necessity of OTC drugs being suitable for self-diagnosis, including the stipulation that "contraindications, interactions, warnings and precautions should be those that can be understood by the consumer". In the assessment, information available to patients – that is, information in package leaflets and on the label, as well as counselling from pharmacists and other health care professionals – should be taken into account. As regards the written information, it should also be considered whether it is clear enough for patients and sufficient to "substitute for the absence of medical supervision". The EU switch guide further notes that "a high incidence of conditions listed as contraindications, precautions or warnings, or a high rate of usage of interacting drugs in the population, in case of patients likely to use the medicine, may increase the incidence and risk of misuse". Other criteria set out that prescription status of drugs should not be

lifted if there is known incorrect use, if there is insufficient post-marketing experience, if they are intended for parenteral application or if provisions on Rx status that are laid out in EU Directive 2001/83/EC are met. In addition, the EU switch guide stipulates that OTC availability can be restricted to a certain dose or a certain pharmaceutical form, or be subject to other restrictions (55).

In the United States of America (USA), more explicit switch criteria were formulated by the former director of the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research in 1989, referred to as 'Peck's principles', in the form of the following 13 questions:

- (i) "Does the switch candidate have special toxicity in its class?",
- (ii) "Does the switch candidate have a large margin of safety?",
- (iii) "Does the candidate's frequency of dosing affect its safe use?",
- (iv) "Has the candidate's safety profile been defined at high dose?",
- (v) "Has the candidate been used for a sufficiently long time on the prescription market to enable the full characterization of its safety profile?",
- (vi) "What is the worldwide marketing experience of the switch candidate?",
- (vii) "What foreign countries market the candidate OTC? What is the experience in those countries?",
- (viii) "What do the 'use data' show?",
- (ix) "Has a vigorous risk assessment been performed?",
- (x) "Has the efficacy literature been reviewed in a way to support the expected usage and labelling of the switch candidate?",
- (xi) "Is there a full understanding of the pharmacy-dynamics [sic] of the switch candidate?",
- (xii) "Is the minimally effective dose for the proposed OTC indication known?" and
- (xiii) "Have possible drug interactions for the switch candidate been characterized?" (56).

In 1998, an additional set of criteria was presented by the then director of the US Food and Drug Administration's Office of Drug Evaluation, which are referred to as the 'DeLap principles' (56). The switch criteria are subdivided into three aspects: 'fundamentals', 'points to consider' and 'safe product use'. Fundamentals include the following questions:

- (i) "Can the condition be adequately self-diagnosed?",
- (ii) "Can the condition be successfully self-treated?" and
- (iii) "Is the self-treatment product safe and effective for consumer use, under conditions of actual use?".

Under the category of points to consider, these questions are listed:

- (i) "Is there a need for physician evaluation of the condition?",
- (ii) "What is the nature and severity of adverse effects of consumer misdiagnosis and delay in correct diagnosis?",
- (iii) "Regarding effective product use, what is the nature of consumer understanding of product use?",
- (iv) "What is the consumer understanding of the expected benefit?" and
- (v) "Does the consumer have the ability to assess the treatment effect?".

The questions regarding safe product use are:

- (i) "What is the consumer understanding of product directions for safe use?",
- (ii) "What is the consumer understanding of what to do if the product is not working?",
- (iii) "What is the consumer ability to identify adverse effects, and the consumer ability to determine when adverse events may require professional care?" and
- (iv) "What is the consumer expectation of safety?" (56).

When comparing the two sets of guiding questions for Rx-to-OTC switches, it becomes obvious that Peck has put more emphasis on pharmacological attributes, whereas DeLap has a stronger focus on consumer attitudes and behaviours. Both lists can thus be seen as complementary to each other.

In 2017, a group of Indian researchers compiled a list of Rx-to-OTC switch criteria as follows: "The symptom intended to be treated by the drug must be one that can be easily recognizable by an individual of average intelligence". (ii) "The drug must possess a very high safety margin". (iii) "The drug must be used for easily recognizable conditions". (iv) "The drug must be easy to administer". (v) "The drug must exert its effect rapidly post-administration and the effect must be easily noticeable". (vi) "The drug must not be addictive or narcotic in nature". (vii) "The use of the drug must not mask any underlying potentially dangerous conditions". (viii) "The treatment regimen must be uncomplicated enough for a layman". (ix) "The drug must not be parenterally administered" (57). Their list was partly based on the World Health Organization (WHO) Guidelines for the Regulatory Assessment of Medicinal Products for use in Self-Medication (57, 58). The latter also expand on the need for sufficient use data prior to assessing an Rx-to-OTC switch application, noting that adverse events should not represent a cause for concern, the need for adequate labelling and a pharmacist's advice and the consideration of the benefits of OTC status. Moreover, the guidelines include a list of risks arising from OTC status and state that switch decisions should be such that these risks are mitigated. In addition, they suggest giving consideration to whether the indication is suitable for self-diagnosis, whether it provides "reliable and consistent relief of symptoms" and whether the drug has

a favourable risk/benefit ratio, and note that the general toxicity, reproductive toxicity and carcinogenicity should be considered in switch decisions. The guidelines also stipulate that there should be a wide margin of safety, an “acceptable level of risk from inappropriate use”, low and well-documented risks for special population groups and a “low or well-characterized incidence of adverse effects” (57).

It should be noted that the US principles, the considerations set out by the German BfArM officer and the list compiled by the Indian researchers were formulated by individuals or groups of individuals, and – unlike the WHO guidelines and possibly the EU switch guide – do not represent the outcome of a consultative process among experts and civil society, or similar (53, 55-58). However, unlike the German, European and WHO criteria, the Peck and DeLap principles have been subject to further public health research (59, 60).

3. OTC drug use in Germany

Unlike the use of prescription drugs, OTC drug use cannot be estimated from routinely collected data via SHI funds (61). Sales data, in turn, are more easily available from companies that specialize in collecting such data (62). As described above, sales data from other countries can be submitted to the BfArM in support of applications for changes to a drug’s trade status (9). At the same time, it is known that sales data can only serve as a rough estimate of the amount of OTC drugs that are actually being used.

Approximations of OTC drug use prevalence – that is, the prevalence of self-medication – have been studied through health survey methods in Germany since the late 1980s. For instance, Tennis analysed the seven-day self-medication prevalence among study participants at the Augsburg study site of the MONICA study. During face-to-face interviews with the study team, participants were asked about their medication use in the previous seven days and whether the drugs they had used were prescribed or self-medicated. He found seven-day self-medication prevalences of 16.5% among women and 9.8% among men aged 30–64 years (63). The German Federal Health Survey of 1998 (BGS98) found a seven-day prevalence of 35.1% of self-medication among German adults aged between 18 and 79 years (64). The Study of Health in Pomerania also collected data on self-medication in the first phase of the study in 1997–2001 (65), but no results have been published so far. In 2013, self-medication in the study population of the first phase of the German Health Interview and Examination Survey for Adults (DEGS1) was analysed, where a seven-day prevalence of

38.8% was found (66). As regards OTC drug use among German adults, the North-Rhine Westphalia (NRW) State Public Health Service conducted a telephone survey to study OTC drug use among adults within NRW. It found a four-week prevalence of OTC drug use of 38.5% (67).

While self-medication and OTC drug use are often used interchangeably in everyday language, these two expressions should not be considered synonyms (61). 'OTC drug use' refers to the use of drugs that are available for purchase without a prescription, which is a legal classification of trade status. Self-medication can refer to the use of OTC drugs, but it can also entail the use of drugs previously prescribed to oneself or to someone else, or self-medication with products that cannot be classified as drugs (68). In addition, previous epidemiological studies measuring self-medication have relied on self-reported information about how the participants say they have obtained the drug (63, 64, 66). An assessment of OTC drug use should instead focus on the trade status of a drug that can be determined objectively (61).

In the context of this thesis, two approaches were pursued to estimate the prevalence of OTC drug use. For that purpose, no distinction was made between pharmacy-only OTC drugs and those on general sale (61, 62). In a first step, an online survey with 300 participants from across Germany was conducted. The online survey used a stratified sampling approach with strata for age, gender and education. Survey participants were asked whether they had used an OTC drug – defined as a drug that was purchased in a pharmacy without a prescription – in the seven days prior to filling in the survey questionnaire. The survey found a prevalence of 46.3% of total OTC drug use, with 40.8% among men and 52.0% among women (62).

As a second approach, seven-day OTC drug use prevalence was calculated based on the DEGS1 dataset; the same dataset that had been used by other researchers to estimate the seven-day prevalence of self-medication (61, 66). The DEGS1 study had a total sample size of 8152 participants representative of the adult population living in Germany (66). A sub-sample of 7091 participants completed the drug information interview. In that interview, study participants were asked about drugs and other health products they had been using during the previous seven days. Based on the information obtained about the drugs used – such as the Pharmazentralnummer (German identification number for pharmaceutical products, PZN), the name, the pharmaceutical company, the pack size and the pharmaceutical form – the actual trade statuses of the reported drugs were determined. As a result, a seven-day OTC drug use prevalence of 40.2% was found in total, including 33.2% among men and 47.2% among women (61).

The analysis of the DEGS1 dataset also sought to identify predictors of OTC drug use through logistic regression analysis. It was found that women were 1.64 times more likely to have used at least one OTC drug in the previous seven days than men. Similarly, people with two or more conditions that are of chronic nature or can require long-term systemic drug treatment were 1.52 times more likely to have used an OTC drug in the previous seven days than those who are not affected by multimorbidity. Likewise, Rx drug use in the previous seven days was a predictor for OTC drug use in the same time span, with an odds ratio of 1.3. Good, mediocre, poor and very poor self-reported health were also identified as strong predictors for OTC drug use, with odds ratios ranging between 1.50 and 4.16 when compared to those who rate their own health as very good. All these findings were statistically significant. Moreover, higher age was identified as a statistically significant predictor of OTC drug use in the previous seven days, with odds ratios of 1.59 and 2.14 for people aged 60–69 and 70–79 years, respectively (61).

4. Changes to drug trade statuses in Germany 2006–2015

With about half of all packs sold in German pharmacies being OTC drugs (69), they form a substantial part of the pharmaceutical supply of the German population. However, changes to OTC drug trade statuses in Germany have hardly been studied previously. Helmstaedter compiled lists of Rx-to-OTC switches and OTC-to-Rx switches in Germany between 1971 and 1985 (70), and Wessels did so for the time frame between 1990 and 2000 (71). The German Medicines Manufacturers' Association published an overview of Rx-to-OTC and OTC-to-Rx switches between 2005 and 2017 (72). The Association also publishes industry-oriented information material on switch procedures in Germany (73).

However, findings from empirical research on German switch procedures have not been available prior to the studies undertaken in the context of this thesis. In order to study recent changes to drug trade statuses in Germany in greater depth, two approaches were pursued: first, unsuccessful applications to increase or decrease the OTC availability of drugs in Germany between 2009 and 2014 were analysed (74). Second, successful Rx-to-OTC switches between 2006 and 2015 were studied in the light of the pharmacological properties of the switched substances or combinations of substances (12).

For the first study, applications for Rx-to-OTC switches, increases in OTC availability, decreases in OTC availability and OTC-to-Rx switches were considered unsuccessful if the EAC recommended that the

application should not be approved or if the application received a positive EAC recommendation which was subsequently not followed by the Ministry of Health and the Bundesrat. An 'increase in OTC availability' was defined as a case where a substance was already available as an OTC drug and the application sought to expand this OTC availability in terms of higher doses, additional user groups, additional indications, other routes of administration, etc. Similarly, a 'decrease in OTC availability' was defined as a case where a substance was already available as an OTC drug at the time of application and the applicant sought to reduce this OTC availability in terms of dose, pack size, indication, etc., although acceptance of the application would not yet result in Rx status.

Between 2009 and 2014, 26 applications for Rx-to-OTC switches were submitted. Of these, the EAC recommended accepting the application in 15 (58%) cases and recommended rejecting the application in eight (31%) cases. No decision was made for three (11%) applications – in two cases because the initial applications were amended and only the alternative applications were voted upon, in one case because the EAC requested additional data. In the same time frame, 12 applications for an increase in OTC availability were made, of which seven were recommended for acceptance and five were recommended for rejection by the EAC. Between 2009 and 2014, 33 applications for a decrease in OTC availability were made, for which the EAC recommended acceptance in 13 and rejection in eight cases. For twelve of the 33 total applications to decrease OTC availability, no decision was made by the EAC or the decision was postponed (74). No decisions were made where alternative applications were accepted through which a decision on the other applications became redundant (75). In one case, a decision was postponed because more data were requested (76) and in other cases because it was decided to hold a dedicated session on pack size restrictions of analgesics at a later stage (45). In addition, there were 13 applications for OTC-to-Rx switches from 2009 to 2014. Of these, the EAC recommended accepting the application in eleven cases and rejecting it in two cases. The German Ministry of Health and the Bundesrat did not follow the positive recommendations by the EAC regarding five applications for Rx-to-OTC switches and regarding nine applications for a decrease in OTC availability (74). An illustration of the fate of the 26 applications is provided in annex II on p. 75.

The most common reasons for the Ministry of Health and the Bundesrat not following positive EAC recommendations were of a legal nature. Only in one case was the decision based on a drug safety concern: an Rx-to-OTC switch application for ipratropium bromide for intranasal use for the treatment of rhinitis received a positive recommendation from the EAC, but the Ministry of Health and the Bundesrat found that the recommendation could not be transposed into law due to insufficient overall usage experience data. It should be noted, however, that an application for an Rx-

to-OTC switch of ipratropium bromide was resubmitted at a later stage, for which the EAC provided a negative recommendation on the same grounds (74).

Reasons for negative recommendations by the EAC were more diverse. As regards applications for Rx-to-OTC switches or for an increase in OTC availability, a lack of suitability for OTC status or other safety concerns were common arguments. Examples included pharmacy staff and patients being unable to exclude a drug's contraindications, the risk of delaying diagnosis of serious diseases due to OTC availability of the substance, inappropriateness of the pharmaceutical form for OTC status and or the existing OTC availability of comparatively safer substances for the indication in question. Other types of argument used by the EAC when recommending rejecting Rx-to-OTC switch applications or applications for an increase in OTC availability were insufficient safety data or a lack of quality of the submitted materials. Concerning applications for decreases in OTC availability, the EAC recommended, for instance, rejecting applications for pack size restrictions of non-steroidal anti-inflammatory drugs to four days. The reason for these recommendations were that the EAC needs to make evidence-based recommendations, and there is no evidence that pack size restrictions increase compliance with the maximum duration of use for OTC drugs. It should be noted, however, that the EAC has recommended such pack size restrictions on other occasions. The EAC provided a negative recommendation on an application to decrease the OTC availability of pancreatin because it felt that the application was motivated by regaining SHI reimbursement and the EAC is not mandated to deal with reimbursement issues (74).

An application for an OTC-to-Rx switch of paracetamol received a negative recommendation because, despite its rather low therapeutic index for the OTC context, EAC members argued that paracetamol is the most frequently sold OTC analgesic in Germany and it comes with the benefit of being the only OTC analgesic and antipyretic licensed for use during all stages of pregnancy and in infants. An application for an OTC-to-Rx switch of pseudoephedrine received a negative recommendation because EAC members found that it was not financially rewarding to use pseudoephedrine from finished medicinal products in illegal drug production (74).

The second study on changes to drug trade statuses in Germany that was conducted in the context of this thesis looked at successful Rx-to-OTC switches between 2006 and the spring of 2015, and investigated the pharmacological properties of the switched substances. Ten substances or combinations of substances were switched in that time period in total. Three of them were substances that were made available OTC only for midwives and naturopaths for use in their professional contexts. One substance was switched in order to correct a clerical error made earlier in the process of revising the German drug law. The other switches regarded the following substances or combinations of substances: Almotriptan, omeprazole, benzydamine,

ibuprofen/pseudoephedrine, racecadotril, ketotifen and levonorgestrel. All of these Rx-to-OTC switches came with restrictions to either certain indications or low doses, small pack sizes, maximum duration of use or other restrictions. When studying the pharmacological properties of the substances in the light of the EU switch guide, it was found that most of the substances were for the treatment of predominantly acute conditions, whereas others were intended for the treatment of acute but often recurring conditions, such as migraine and seasonal allergic conjunctivitis, or – as in the case of omeprazole – for the treatment of acute conditions that can also take chronic courses. Moreover, it was found that some of the switched substances might interact with commonly used drugs, potentially resulting in serious ADRs – such as almotriptan interacting with selective serotonin reuptake inhibitors and selective serotonin noradrenalin reuptake inhibitors, potentially causing serotonin-like symptoms, or ibuprofen/pseudoephedrine interacting with other non-steroidal anti-inflammatory drugs, potentially resulting in an increased risk of gastrointestinal ulcerations and bleeding. It was also found that some of the switched substances had contraindications, precautions and warnings that concern substantial parts of the population, such as a history of myocardial infarction or present coronary heart diseases in the cases of almotriptan and ibuprofen/pseudoephedrine (12).

5. Perceptions of OTC drug safety among German adults

In the light of the significant prevalence of use of OTC drugs among German adults, journalists and scientists expressed concerns in the early years of this decade about possible misuse and abuse of OTC drugs, and that such behaviours were being fostered by patients' perception of OTC drugs as low-risk products (77-79). In order to examine such claims in a more empirical manner, the work of this thesis sought to examine risk perceptions regarding OTC drug use in Germany. For this purpose, the above-mentioned online survey of 300 participants conducted in 2013 also included questions on risk perceptions of OTC drugs and consumer behaviours (62).

It was found that study participants had balanced views towards the risks of OTC drugs and showed good knowledge of the various pharmaceutical forms and routes of administration of OTC and Rx drugs. The perceived safety of OTC drugs was significantly lower among people who reported never having used OTC drugs and among people aged 60 years and older. When asked to rate the perceived safety of specific OTC products, those for dermal application and plant-based products were considered safer than products for oral use and chemically synthesized substances. It was also

found that participants tended to judge a specific OTC drug as less risky if they reported having used that drug previously. In addition, the survey questionnaire prompted participants to share what they understood by OTC drug safety. They could select one or multiple answers, or write their own definitions. The four most common replies were: (i) “effectiveness when used for the right reason”, (ii) “low probability of side effects when used correctly”, (iii) “risks and benefits of drug use are proportionate” and (iv) “material purity of the drugs’ components” (62).

Furthermore, the survey sought to study certain behaviours regarding OTC drugs. For example, 17.7% of participants reported having ever used OTC drugs off-label, with a statistically significant higher proportion among participants below 60 years of age. OTC drug risk perception and OTC drug off-label use, however, were not associated in a statistically significant manner. Regarding package leaflet reading habits, 48.0% of the survey participants reported always reading the package leaflets of OTC drugs, 44.5 % reported not reading them if they knew the drugs or believed that the drugs were very safe. The most common reason for not reading the package leaflets among the 3.7% of participants who reported never reading them was: “advice from the pharmacy is sufficient for me”. Among those who read OTC drug package leaflets always or under certain conditions, information on dosage was read most often, followed by information on contraindications and interactions (62).

6. Discussion

Although the topic of OTC drug use and regulation is hardly mentioned in standard public health literature (80, 81), it can be considered as a model example of a public health issue in the German context. That is because OTC drug use concerns a significant proportion of the population living in Germany (61) and because drug regulation is a public task in itself, which has already been explained in the background chapter.

According to a common definition, public health is “the science and art of preventing disease, prolonging life and promoting health through the organised efforts of society” (82). Along these lines, Gillam et al. distinguish between ‘the science of public health’ and ‘the art of public health’. The science of public health refers to the different disciplines such as medicine, epidemiology, demographics, psychology, sociology, ethics, political sciences and others which are used to assess the state of population health and underlying causes as well as identifying possible solutions and interventions. The art of public health in turn, refers to the task of implementing solutions that will effectively improve population health and health care (83).

As a piece of scholarly work, the present thesis makes a contribution to the science of public health, in particular as regards the empirical findings presented in chapters 3-5 and the methodological reflections in section 6.1. The subsequent sections of the following discussion should be considered as a contribution to the science of public health as well, but have been written with the art of public health in mind. In order to bridge these two streams of the public health discipline, recommendations derived from the discussion in sections 6.2-6.4 do not only expand upon future research needs, but also include considerations for improving public health practice regarding OTC drug regulation in Germany.

Next to the distinction between the art and the science of public health, the discipline is generally considered to have three large domains: Health protection, health promotion and health services research, which has been explained in the introduction. The interlinkages between OTC drug regulation and the different public health domains will be explicitly discussed in section 6.4.

6.1 Methodological reflections

Public health is a multidisciplinary field, as population health is determined by biological, environmental, lifestyle and health care organizational factors at the individual, community and societal levels (78, 79). Therefore, qualitative, quantitative and mixed methods are used to study public health issues from multiple angles. Accordingly, the studies on which this thesis is based have made use of multiple methods to study OTC drug use and OTC drug regulation, as well as perceptions and behaviours regarding OTC drugs (12, 61, 62, 74).

The application of qualitative methods such as the content analysis of EAC session minutes and their supplementary materials, as well as policy and legislative documents, forms a suitable approach to study questions such as the number of successful and unsuccessful switch applications and the reasons behind unsuccessful applications to increase or decrease OTC availability. Using content analysis to study the number of applications to change drug trade statuses and their respective fates is highly objective and reproducible. The analysis of reasons for unsuccessful applications was, however, limited by a lack of information in the session minutes and other documents, as regards both considerations behind the recommendations made by the EAC and reasons that the Ministry of Health did not follow a recommendation, as these were not always explicitly provided in the documents analysed. Especially regarding EAC recommendations, it was not always clear how strongly the different arguments had been weighed towards a negative recommendation for a

change in trade status (74). As an alternative or to complement the methods used, qualitative interviews with EAC members could have been considered, but these would have been difficult to implement as members are obliged to maintain confidentiality about the deliberations during EAC sessions. Further, no specific methods to validate results from qualitative methods, such as triangulation, were applied in the context of the study due to resource constraints. In order to enable better scientific analysis of the reasons for unsuccessful applications for changes in drug trade statuses through content analysis in the future, it would be helpful if the BfArM provided as much detail for negative recommendations in its EAC results reports as it does for positive recommendations.

The case-study approach to studying the pharmacological properties of substances and combinations of substances that have been switched from Rx to OTC status – taking into consideration the documents mentioned above, the SPCs of the respective products and the EU switch guide – is an appropriate method to address the question of how far the stipulations in the EU switch guide meet the actual pharmacological properties of the switched products. Limitations of the study were that some stipulations in the EU switch guide are not clearly defined and that some ADRs listed in the SPCs cannot be clearly assigned as ‘serious’ or ‘not serious’; these therefore required discretionary decisions by the researchers, which were applied in a consistent manner (12).

In order to study the prevalence of OTC drug use, two approaches were used in the context of this thesis. Initially, an online survey was conducted with 300 adult German participants. Online surveys provide significant advantages in terms of time and cost when compared to other survey methods (84, 85). At the same time, they involve a number of limitations. Most importantly, adequate sampling is an issue which was also faced when conducting the online survey for this thesis. An appropriate sampling technique is usually chosen aiming to achieve the highest level of representativeness of the population on the one hand, balanced against several aspects of practical feasibility on the other hand (86, 87). For example, a sample size of 384 participants is considered adequate when aiming at a 95% confidence level and 5% margin of error assuming a simple random sample (87). However, the sample used for the online survey conducted in the context of this thesis was limited to 300 participants due to limited financial resources. In order to mitigate this shortcoming, a quota sampling approach was used to ensure adequate representation of different age, gender and educational groups (62). As with other types of surveys, non-response error is relevant to online surveys and thus presents another limitation of the study. For example, people without internet access are systematically excluded from online surveys and it can be assumed that people who participate in online surveys differ from those who do not. It is also known that people

are more likely to participate in online surveys if they are interested in the topic of the survey and/or have a general appreciation for the advancement of science (88).

Whereas the online survey thus came with multiple challenges regarding sampling and accordingly limited representativeness (62), the analysis of DEGS1 data was the first study of OTC drug use in a representative sample of the adult population living in Germany (61). DEGS1 is a publicly funded study that builds on previous long-lasting experience of representative federal health surveys in Germany. The DEGS1 data were obtained over a three-year period by the German Federal Public Health Institute: the Robert Koch-Institut (RKI) (89). In order to ensure representativeness, a two-stage stratified cluster sampling approach was used. In a first stage, 180 administrative communities called 'sampling points' were selected. Of these, 120 had already been sampling points during the BGS98. All potential sampling points in preparation of BGS98 and DEGS1 had been stratified according to the size of their adult population. In that way, sampling points were selected randomly, but the probability of being selected was proportionate to their population size. Within each selected sampling point, participants were selected randomly, but stratified for age groups. Participants of BGS98 were re-invited into the sample of DEGS1 (90). A limitation of the two-stage cluster sampling approach is the so-called 'design effect', which describes the difference in variance between a cluster sample and a simple random sample in the same baseline population. The design effect can usually be reduced by including more sampling points and fewer participants per sampling point. However, this consideration needs to be traded off against practical limitations. In order to address the design effect introduced through the two-stage cluster sampling approach in the analysis, a weighting factor was created for DEGS1, which was also applied during the analysis of OTC drug use conducted in the context of this thesis. In addition, the organizers of the DEGS1 study made multiple efforts to reduce non-responses, such as offering appointments during early mornings and evenings, telephone follow-up with people who had been invited to participate but did not react to the invitation and the translation of questionnaires in other languages (89).

For the drug information interviews, the so-called 'brown bag' method was used (91). That is, study participants were told to bring all packs of medication, dietary supplements, etc. that they had used in the previous seven days to their appointment with the DEGS1 interviewers. Each pack the participants brought was then scanned or manually entered during the computer-assisted interview (61). The brown bag method offers the advantage of reducing the risk of limited recall by participants, compared to simply questioning them about which drugs and products they have used prior to the appointment (91). Also, where participants did not bring all the products used, they were further asked to complete the drug information questionnaire at home and to send it to the DEGS1 study team. Where such a requested questionnaire was not received, the study team conducted a

follow-up by phone or letter to increase the completeness of the information (92). The brown bag method, the face-to-face interviews and the follow-up measures of the drug information interview therefore constitute a strength of the DEGS1 study. For the purpose of this thesis, however, the fact that the drug information interview was not explicitly designed to study OTC drug use represented a weakness. As the trade statuses of the products in question had not been recorded during the data collection phase, they had to be derived from other information gathered, such as the PZN, the name, the pharmaceutical company, the pack size and the pharmaceutical form. On that basis, the trade status of each product was carefully assessed, by comparing the above-mentioned information provided for each reported product with annex 1 of the Ordinance on Prescription-Only Medicines and other literature and databases where necessary –permitting a differentiated analysis of OTC and Rx drug use which previously could not be done (61).

With 7091 participants in the drug information survey, the two-stage cluster sample, the applied weighting factor and the efforts to increase the participation rate, the results of the analysis of DEGS1 data are much stronger in terms of sampling and linked representativeness compared to the online survey conducted at the outset of the research for this thesis. However, there are also substantive differences in the resource needs for both approaches. The online survey nonetheless provided valuable insights. First, as the time period between data collection and results publication was short, it allowed better conclusions on recent developments to be drawn. Second, due to its narrow focus on OTC drug use, attitudes and behaviours, it provided an opportunity to put epidemiological analyses in a broader public health context, including formulation of strong recommendations for possible future research.

6.2 Improving the evidence base for switch decisions using available data

As highlighted in section 2.5, not much strong normative guidance on switch criteria is available. However, when considering the current thinking from Germany, at the EU level, from WHO and from the USA, it could be argued that in order to increase the evidence base of EAC recommendations, a lot of additional data and thus research would be necessary in order to substantiate each single switch decision. However, while a stronger evidence base for health protection decisions is always desirable, such a requirement needs to be carefully balanced against the associated costs. Regarding the German situation in particular, it could even be argued that a general request for additional data is at odds with two particularities of the German framework for switch decisions. First, as switch

decisions in Germany are substance-based, it may not always be possible to ask a particular licence holder to fund and conduct additional research, as a switch decision may or may not benefit different pharmaceutical companies in different ways. As was shown by Stähler in the context of the European centralised switch procedure, there is an expectation among licence holders who invest in additional research supporting decisions on OTC availability that they will be able to market their product under OTC status exclusively for a certain period in order to recover their additional research costs (37). Second, the fact that any natural or legal person can submit an application for a change in trade status would be undermined if it needed to be supported by a substantial additional amount of data, which a public agency, an individual or a civil society organization might not be able to deliver.

Nonetheless, there is certainly scope for improving the evidence base for switch decisions by synergizing different public interests rather than trading them off against each other. As was pointed out in this thesis, the BfArM serves as a secretariat and provides scientific support to the EAC (6), while the RKI regularly conducts large-scale surveys on population health, including on drug use (89). As both institutes operate under the aegis of the German Ministry of Health (93), it would be beneficial to make the dataset of, for example, DEGS1 available to the BfArM. If the BfArM then had capacity to analyse these data in the light of specific applications for changes in trade status, a number of stipulations that can be found in the EU switch guide could be substantiated with better evidence. For example, the prevalence or incidence of “conditions listed as contraindications, precautions or warnings” could be calculated in many cases, if not already available from RKI publications. Similarly, the actual “rate of usage of interacting drugs in the population” could be assessed. To a limited extent, “known incorrect use” (55) could also be calculated, provided that information on indications was available, which is currently not the case due to data quality concerns. These empirical findings could then inform the deliberations of the EAC. Moreover, regular health surveys conducted by the Länder (federal states) could be used to include questions regarding social or behavioural factors that may be pertinent to single switch decisions or to OTC drug use in general.

Another issue that is highly relevant to questions of changing drug trade statuses is the quality of advice provided in pharmacies. Several state pharmacy chambers [Landesapothekerkammern] regularly commission so-called ‘pseudo-customer’ or ‘mystery shopping’ surveys, to assess the quality of counselling in community pharmacies (94-98). The results of such studies could also be useful in informing decisions on changes to trade status, but they currently seem not to be shared with the BfArM or EAC members. In addition, there have also been a few scientific mystery shopping/pseudo-customer studies in German pharmacies (99-101), which could be useful to EAC deliberations as well. However, none of the EAC meeting documentation analysed in the context of

this thesis made reference to such studies. Instead, the EAC tends to make assumptions about clients' interactions with pharmacy staff. One such example is the Rx-to-OTC switch of almotriptan, for which OTC status was recommended "for the acute treatment of the headache phase of migraines with and without aura in adults between 18 and 65 years, after an initial diagnosis by a physician ..." (12). In that case, the EAC presumed that pharmacy staff would ask the age of the client and inquire whether they had received an initial diagnosis of migraine by a physician, although there is no evidence that this is the case.

Obviously, neither the quality of counselling in pharmacies nor the level of patient compliance in the OTC context can be known for a specific drug prior to its change in trade status. It would therefore be advisable that decisions on drug trade statuses should be reviewed after several years of implementation. Then, pharmacovigilance data that was obtained under the new trade status could be analysed and, if available, studies on pharmacy counselling and behavioural aspects of patients could also be included. Such a review would not need to be comprehensive for all previous EAC recommendations: even a sample of decisions for post-switch review could be of added value for future EAC deliberations.

6.3 Systematic approaches to support the decision-making process for changes in drug trade statuses

It is a recognized paradigm of the science of decision analysis that the quality of a decision itself cannot be judged at the moment it is made, as the outcome – that is, the consequence of that decision – will not yet be known. Instead, the quality of the process that has led to a decision can be assessed and is thus the actual subject of study in decision analysis (102). To this effect, none of the research conducted in the context of this thesis was intended to study whether decisions to change the trade statuses of drugs were appropriate. Rather, aspects of the process of decision-making by the EAC and the Bundesrat were looked at when the pharmacological properties of substances that had been switched from Rx to OTC status were studied against the stipulations of the EU switch guide or reasons for negative decisions on changing trade statuses were analysed. In this section, a number of such considerations will be discussed from a normative-factual perspective.

OTC drugs should not be for parenteral application according to EU legislation, the EU switch guide, the WHO guidelines and the considerations behind the recommendations of the EAC (32, 53, 55, 57). However, there are OTC drugs on the German market where this provision is not met, such as

cyanocobalamin 1000 µg for the treatment of vitamin B12 deficiency – for intramuscular or intravenous injection (103). Similarly, there are a number of homeopathic preparations which are intended for parenteral application which have OTC status as well (104).

Effectiveness is another recurring topic in the suggested considerations for OTC availability. In Brixius' (the BfArM officers') reflections during the inaugural EAC session, for instance, she referred to the risk of "unintentional overdosing ... e.g. due to a lack of effectiveness" (53), which is an argument that was indeed used in practice when the EAC recommended not to switch the antimigraine drug sumatriptan from Rx to OTC status, where the EAC found that its strong variability in the onset of action makes the drug unsuitable for the self-medication of acute migraine attacks (76). However, a similar argument could be made for the antihistaminic drug doxylamine for the short-term treatment of sleeping disorders: it is available as an OTC drug in Germany, where patients may consider taking a second dose earlier than recommended if they do not experience an effect after the initial drug intake. One may also argue that the elimination half-life of 10.1 hours of doxylamine (105) is rather long for an OTC drug that is foreseen to be used in a 24-hour interval (105), especially when considering one of Peck's (the former FDA directors') principles: "Does the [switch] candidate's frequency of dosing affect its safe use?" (56). It is well known that regulatory decision-making on OTC status in the USA puts more emphasis on conditions of actual use both in terms of normative considerations as well as regarding the evidence required compared to European regulators (37, 106). Acknowledging that certain aspects of OTC regulation cannot simply be transferred from one country to another, as OTC drug use happens in the greater context of different health care systems, European regulators may nonetheless wish to raise questions regarding actual use more often. In the context of OTC H1-antihistamines to treat insomnia, for instance, French researchers found that patients are generally compliant with dosing instructions, but not as regards maximum duration of use (107).

When studying the proposed considerations for OTC status mentioned above, the stipulation that OTC drugs should have a large therapeutic index is very common (53, 56-58). This consideration is sensible, since OTC drugs should still be safe in cases of overdosing. At the same time, paracetamol, which has a rather narrow therapeutic index, is among the most traditional and popular OTC drugs. In the context of this thesis, it has been shown that an OTC-to-Rx switch application regarding paracetamol made reference to its narrow therapeutic index but received a negative recommendation by the EAC. The EAC argued that paracetamol is still the safest analgesic and antipyretic for use in infants and during pregnancy. At the same time, it cannot be denied that suicides are committed through intentional paracetamol overdosing (74). Against this background, pack sizes have been restricted to a maximum 10 g of paracetamol in Germany since 2008 (108). The

effects of such measures on both intentional and unintentional overdoses remain subject to further research needs (74), as well as the questions of the extent to which suicide attempts with paracetamol can be prevented by regulating trade status alone and of how far pharmaceutical practice (counselling and selling), public mental health interventions (e.g. campaigns that encourage people with depressions to seek help) and the safe storage of OTC drugs at home could contribute to improving the situation.

Furthermore, the EU switch guide states that OTC drugs should have “no interactions with commonly used medicines which can produce serious adverse reactions” and that a “high rate of usage of interacting drugs in the population, in case of patients likely to use the medicine, may increase the incidence and risk of misuse”. These considerations present a useful precautionary measure at the population level. However, the research work underlying this thesis has shown that, depending on the definitions of “serious adverse reactions” and of “high levels of use” (55), this stipulation is not always met – for example, as in the case of almotriptan, which interacts with e.g. selective serotonin reuptake inhibitors which can result in serotonin syndrome-like symptoms (12). In addition, it can be argued that this stipulation is largely based on assumptions. For instance, it assumes that there is significant overlap between the users of the OTC drug in question and the users of the interacting drug. Moreover, it assumes that OTC drug users would not inform pharmacy personnel about other drugs used and/or that pharmacy personnel do not enquire about them. The latter is particularly interesting considering that in the context of the Rx-to-OTC switch of almotriptan, it has been assumed that pharmacy personnel would inquire rather extensively about possible risk factors (12).

In addition, the WHO guidelines and the EU switch guide mention as one risk of OTC drug use the masking more severe underlying conditions and the related risk linked of delaying diagnosis thereof (55, 57). This consideration was addressed in the Rx-to-OTC switch of omeprazole, where the OTC availability was restricted to a certain pack size and a maximum duration of use of 14 days (12). However, the questions of whether an OTC switch candidate may mask more serious diseases, the potential consequences thereof and how such risks can be mitigated in the OTC context are not systematically raised and addressed in the initial assessments of the BfArM or during EAC deliberations.

Except in the WHO guidelines, the question of whether OTC availability would be beneficial to the population has not been raised in the normative considerations presented above. However, when reasons for negative EAC recommendations, including for OTC-to-Rx switches were analysed for this thesis, it was shown that benefits from OTC availability – that is, the easier accessibility of OTC drugs – may play an important role in EAC recommendations. Examples of where benefits were

weighed in EAC recommendations include paracetamol, as explained above, as well as the Rx-to-OTC switch of levonorgestrel for emergency contraception in 2014 (74).

Obviously, stipulations from the EU switch guide or other guidance and practical considerations that were made by the EAC in the context of a concrete recommendation cannot easily be compared, as the latter always come with a context and are very specifically tailored to the facts. At the same time, the highlighted discrepancies show that EAC deliberations could, in general, be more systematic. In order to address this shortcoming, a list of key questions could be elaborated in a participatory process, which could be based on a synthesis of considerations in the EU switch guide and similar listings, as well as the question of benefits of OTC availability, which could then be used to guide EAC deliberations and document them in a transparent manner.

6.4 Beyond health protection: OTC drugs in the light of health services and health promotion objectives

As outlined in the background chapter of this work, OTC drug regulation, when considered from a drug safety perspective, falls within the public health area of health protection. That field of public health concerns itself with protecting the population from health threats such as communicable diseases, environmental hazards and health hazards from consumer products such as chemicals, foods or drugs (83, 109). However, the new public health – a concept that emerged in the 1990s – represents a paradigm that population health is not merely the responsibility of governments, but that health systems play an important role in striving for good population health, as do health-promoting behaviours by individuals (110). Hence, this section will discuss the topic of OTC drug use and regulation in a broader, new public health context, by addressing its links to health services research and health promotion.

Black & Gruen define health services research as a “multidisciplinary activity to improve the quality, organization and management of health services” (111). Definitions of health promotion are abundant (112), but a recent WHO definition is as follows: “Health promotion enables people to increase control over their own health. It covers a wide range of social and environmental interventions that are designed to benefit and protect individual people’s health and quality of life by addressing and preventing the root causes of ill health, not just focusing on treatment and cure” (113).

The most obvious link between the health protection topic that was addressed throughout this thesis and the subject area of health services research is the fact that OTC drug purchases are coupled with a lack of reimbursement by SHI funds. Although it was shown in the context of this thesis that the Bundesrat does not follow all recommendations made by the EAC, it does so in the majority of cases (74). Every time this is the case for Rx-to-OTC switch decisions, it can be argued that while drug safety issues are subject to the deliberations of the EAC, a de facto decision on reimbursement – or rather non-reimbursement – is also taken when the Bundesrat follows a positive recommendation for an Rx-to-OTC switch or an increase of OTC availability. The Bundesrat makes considerations beyond drug safety before its decision, including economic and other implications for society (114), but it cannot decide to grant OTC status to a substance while keeping it reimbursable by SHI funds. It should also be noted that there is no such automatization as regards OTC-to-Rx switches, that is, a drug does not become automatically reimbursable by SHI funds if it receives Rx status. The question of whether a drug can be reimbursed and under which conditions is subject to a separate decision by the G-BA and drugs newly admitted to the market since 2011 are subject to cost-effectiveness assessments (14, 115, 116).

The close connection between reimbursement and OTC status has several potential implications – for example, for the health system goal to ensure equitable access to care, including to OTC drugs; for health system efficiency; and for the system’s responsiveness to consumer perceptions. These are discussed in the following paragraphs.

As explained in the background chapter, the decision no longer to reimburse OTC drugs was considered socially acceptable due to their average price of eleven euros per pack (18). However, it must not be ignored that there are nonetheless people with low incomes or other financial difficulties who will not be able to afford OTC drugs (117). Drugs in Germany have, apart from a few exceptions, either Rx or OTC status, which means that often patients in need cannot avail themselves of even a medically indicated OTC drug at low cost or no cost. Since there are – unlike for co-payments for drugs that are reimbursable by SHI– no particular tariffs or other social measures (e.g. subsidies, exemptions) in place for OTC drugs that are not reimbursable by SHI, this equity challenge has so far merely been addressed through charitable measures, such as so-called ‘medication banks’, as discussed in the article “Use of over-the-counter (OTC) drugs and perceptions of OTC drug safety among German adults” provided in annex I of this thesis (62).

Closely linked to this topic, it is also conceivable that physicians would prescribe a stronger or higher-dosed Rx drug than the indicated OTC drug to address patients’ affordability concerns where necessary. It would therefore be desirable to conduct further research on whether the coupling of

OTC status and the lack of reimbursement may imply inefficiencies in the public health care system or result in suboptimal pharmacotherapy for poorer population groups (118).

Concerning responsiveness to consumer perceptions, a lack of reimbursement might be associated with a perceived lack of efficacy, in particular since one of the intentions of the SHI Modernization Act was to preclude inefficient therapies from reimbursement. It was shown in this thesis that consumers do not perceive OTC drugs as products without risk (62). However, whether there is a perceived association between OTC status and a lack of efficacy remains subject to further research.

At the same time, it cannot be denied that some OTC drugs are available without sufficient evidence of their efficacy and effectiveness (17). While SHI funds have established a system that evaluates the efficacy of certain treatments, including by comparing them to alternative options in order to choose only cost-effective options for reimbursement (14), the OTC drug market comes with a number of consumer protection issues. For example, applications for Rx-to-OTC switches can be driven by the interests of the pharmaceutical industry, which can be at odds with public interests. A commonly cited example is patent expiry (3, 37, 119), but a drug being excluded from reimbursement by SHI funds may also be a reason for the industry to seek OTC status, as has been argued by one EAC member (120). As OTC status also permits direct-to-consumer advertising (32), there is no additional barrier to protect consumers from possibly ineffective OTC drugs.

Moreover, as regards the interface of OTC status and reimbursement, there is a discrepancy in terms of procedures. Whereas anyone can submit an application to the BfArM for a change in a drug's trade status (9), only licence holders can submit a request to G-BA for their products to be added to the list of exceptions – of drugs that can be reimbursed despite their OTC status (18). However, other stakeholders may also have a legitimate interest to do so, as shown in the article “Unsuccessful applications to increase or decrease the over-the-counter (OTC) availability of drugs in Germany between 2009 and 2014” provided in annex II (74). This original work demonstrated that the German Society of Gastroenterology, Digestive and Metabolic Diseases requested a decrease in OTC availability of pancreatin, which was rejected due to the EAC's perception that the application was made to facilitate reimbursement, for which the EAC is not responsible (74). As well as gaining a better understanding of the advantages and disadvantages of coupling OTC status and non-reimbursement, how far the strictly separate assessments of OTC status on the one hand and of reimbursement on the other hand are beneficial for public health and the shortcomings of this approach should also be researched. Similarly, from a health services research perspective, it could be interesting to conduct more systematic economic evaluations of past decisions of changes in drug trade statuses to better understand their impact and thereby guide future decisions of the Bundesrat, and possibly to inform OTC drug policy in general.

Another aspect of switch regulation linked to health services research regards the risk-reducing measures described in section 2.4. As noted, it is virtually impossible for the EAC to make an Rx-to-OTC switch conditional to a change in the package leaflet or the label due to the interaction between national and EU legislation (42, 44-46); nor can it make binding recommendations on advertising (51). Next to the risk-reducing measures that the EAC does actually have at hand listed above, a popular theme in international research on OTC drug regulation is the consideration of additional trade statuses. In the USA, for example, it is occasionally argued that next to an Rx status and a general sale status there should be a pharmacy-only category (121, 122). As German trade statuses already comprise these three categories, it may be worth exploring an additional pharmacist-only category – which is available, for instance, in Japan (123, 124) – or whether there is a possibility of excluding certain OTC drugs from internet sales, in those cases where personal interaction with a trained intermediary is of particular relevance to ensure the safe use of the OTC drug in question. However, exploring such possibilities would require further research not only in the field of public health, but also in that of law.

Nicotine replacement products are an example of OTC drugs that are linked to questions of both health services research and health promotion. On the one hand, smoking cessation is an important public health goal and is the subject of many health promotion interventions due to its role in the prevention of numerous non-communicable diseases (125). On the other hand, nicotine replacement products are excluded from SHI reimbursement per se, regardless of their trade status (126). Although it has been shown that the effectiveness of nicotine replacement therapy is not affected by whether it is prescribed or purchased at patients' own initiative (127), it should also be considered that most SHI funds subsidize other means of promoting smoking cessation, such as workshops. Conducting an economic evaluation of whether the political decision to exclude nicotine replacement products from reimbursement is actually cost-effective, in the light of the public health goal to prevent nicotine abuse, could therefore be worthwhile (128).

In a similar vein, it could be considered that the seasonal influenza vaccine should be made available without prescription for administration by trained pharmacists in Germany, as is the case, for instance, in the USA (129), New Zealand (130, 131), some provinces of Canada (132) and several cantons of Switzerland (133). As explained in section 2.1 and shown in the article "From prescription-only (Rx) to over-the-counter (OTC) status in Germany 2006–2015: pharmacological perspectives on regulatory decisions" (see annex III) (12), it is possible to make prescription drugs available as OTC drugs for use by health professionals other than physicians in their professional contexts; this has precedents in Germany, such as lidocaine made available for midwives and epinephrine made available for naturopaths (12). The administration of influenza vaccines in community pharmacies is

mainly intended to increase vaccination coverage of the population, which is an important public health goal (130, 132). In Switzerland, it is also part of the national strategy for pandemic influenza preparedness, as it has been argued that in a pandemic incident, community pharmacists can only be relied on for vaccine administration if they are also trained and equipped outside such scenarios (134). The government of New Zealand made similar considerations (130). It is usually argued that longer opening hours and low-barrier access to community pharmacies facilitate vaccination uptake by the population (130, 132, 135) and that this – as with other OTC drugs – lowers the workload of general practitioners (135), saves time for patients (132) and saves costs for the public health care system (129, 136). Scientific evidence about the extent to which these considerations are true is still limited. In New Zealand, it has been shown that 42% of patients who were vaccinated by a community pharmacist had not been vaccinated in the previous season (130). In the USA, vaccination coverage increased significantly over a 10-year time period of vaccinations by community pharmacists (129). In the relevant provinces in Canada, however, the increase in vaccination coverage was only moderate (132, 137), and in a pilot project in London no significant increase in vaccination coverage among groups at risk was observed. The latter project also conducted an economic analysis, which found that the costs per dose administered at a pharmacy are slightly lower than those per dose administered by a general practitioner (136). Similar scientific evaluations from Switzerland are not available to date, although these would be particularly interesting to inform the German situation. Nonetheless, the various findings that were made in different Anglo-Saxon countries show that the extent to which an Rx-to-OTC switch can contribute to achieving a particular public health goal is highly contextual – in particular regarding national health care arrangements – and that findings cannot easily be transferred across countries.

7. Conclusions

This thesis makes a substantial contribution to the existing knowledge about OTC drug use, perceptions and regulation in Germany. It expands upon the public health context of these topics and discusses the implications of the findings for public health research and practice. The research underlying this thesis constitutes the first attempt to measure OTC drug use – the use of drugs that are available for purchase without a prescription – rather than self-medication, in a representative sample of the adult population living in Germany. To date, it is also the only work that has addressed German OTC drug regulation in an empirical manner, by studying the reasons behind unsuccessful applications to change drugs' trade statuses, as well as the pharmacological properties of substances

that were switched from Rx to OTC status in recent years. Furthermore, it comprises research, which has been done for the first time in Germany, that brought together information on OTC drug use and behaviours related to OTC drug use, as well as perceptions of OTC drug safety among adults.

With a seven-day prevalence of 40.2%, it has been shown that OTC drug use among the adult population living in Germany is significant. Despite the large number of users and the important role of OTC drugs in the German health care system, the topic receives rather little attention in public health research and practice. It has been shown that not every EAC recommendation for a change to drug trade status is necessarily transposed into law. While applications for changes in trade status, EAC deliberations and the fates of the applications are rather transparent, which made it possible to study them for this thesis, the reasons for certain recommendations – especially when they are negative – are far less traceable. Against this background, several opportunities for improving OTC drug regulation in practice have been identified: the BfArM and the Bundesrat should provide justifications for negative recommendations/decisions on changes to trade status applications, just as they do for positive ones. Data that are often already available – for instance from large epidemiological studies, routine health surveys or obtained by pharmacy chambers – could be used to inform decision-making on potential changes to drug trade statuses. Large epidemiological field studies that include drug utilization studies should make a distinction between self-medication and OTC drug use and should also collect information on the doses and durations of use of OTC drugs. In addition, past changes to trade statuses should be evaluated so that lessons learned can inform future decision-making. Similarly, whether certain switch decisions require routine reviews after a given number of years should be considered, especially when bearing in mind the finding that higher age was identified as a significant predictor for OTC drug use, as well as the findings on interactions, warnings and precautions, which have not always met the stipulations of the EU switch guide in recent switch decisions. Acknowledging both that EAC recommendations are snapshots and that demographics, drug-use patterns and pharmacovigilance data change over time, an approach consisting of routine reviews could be justified. It is also recommended that the BfArM and the EAC should elaborate a set of criteria that touches upon both the risks and the benefits of OTC availability; this could guide deliberations on applications for changes to drug trade statuses, support their documentation and make them more systematic and transparent. The elaboration of such a set of criteria could also be useful in creating a catalogue of additional research needs to increase evidence-based OTC drug regulation.

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9. Declarations

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte fremde Hilfe angefertigt habe, keine anderen als die angegebenen Quellen oder Hilfsmittel benutzt habe und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

I hereby declare that I have written this thesis independently and without unauthorized external help, that I have not used any sources or aids other than those indicated and that I have provided references for all sources used, either verbatim or in content.

10. Abstract

Introduction: Public health practice must ensure efficient access to effective and safe pharmaceuticals, while protecting the population from health risks related to the inappropriate use of pharmaceuticals. **Background:** About half of all packs sold in German pharmacies are over-the-counter (OTC) drugs; their use and regulation is thus a subject of high relevance to public health. At the same time, OTC drugs receive rather limited attention in the drug regulatory and pharmacological literature, and little empirical evidence is available about OTC drug consumption and risk perceptions. **Scope:** The present thesis is based on four individual research papers that cover perceptions of and behaviours regarding OTC drugs among German adults, reasons for unsuccessful applications for changes to drug trade statuses, pharmacological perspectives on prescription-only (Rx)-to-OTC switches and the prevalence and predictors of OTC drugs use. **Methods:** This research draws on mixed methods, including an online survey, qualitative content analysis of policy and legislative documents and epidemiological analysis of data from the first phase of the German Health Interview and Examination Survey for Adults. **Results:** Among the adult population living in Germany, a seven-day OTC drug use prevalence of 40.2% was found. Female gender, older age, self-reported reduced health status and multimorbidity were significant predictors of OTC drug use. There were seven Rx-to-OTC switches between 2006 and 2015, but not all of these decisions were fully in line with the recommendations of the EU's guideline on changing drug trade statuses. Further, unsuccessful applications for Rx-to-OTC switches, OTC-to-Rx switches and other changes trade status were not infrequent. At the expert level, the most important reasons for rejected applications were drug safety concerns and insufficient data. At the policy level, negative decisions were mainly made because of legal restrictions. It was also found that risk perception of OTC drugs greatly depends on the route of administration and whether the product is plant-based or not. Moreover, consumers do not always read all details in the package leaflet. **Conclusions:** This thesis constitutes the first measure of OTC drug use in a representative sample of the adult population living in Germany. With a seven-day prevalence of 40.2%, OTC drug use is significant. While applications for changes in drug trade status and their fate are transparent, the reasons for negative recommendations are far less traceable. The findings of this thesis have led to the identification of several opportunities to improve OTC drug regulation. Detailed justifications for negative decisions on applications to changing drug trade statuses should be provided. Data that are already available – for instance, from large epidemiological studies – could be used to inform decision-making on potential changes to drug trade statuses. Such studies should make a distinction between self-medication and OTC drug use; they should also collect information on the doses and durations of OTC drug use. In addition, past

changes to trade statuses should be evaluated so that lessons learned can inform future decision-making. Elaboration of a set of criteria concerning the risks and benefits of OTC availability is also recommended to increase evidence-based OTC drug regulation.

11. Zusammenfassung (auf Deutsch)

Einleitung: Die Public-Health-Praxis bzw. das öffentliche Gesundheitswesen muss einen adäquaten Zugang zu wirksamen und sicheren Arzneimitteln gewährleisten und dabei die Bevölkerung gleichzeitig vor Gesundheitsrisiken durch inadäquaten Medikamentenkonsum schützen.

Hintergrund: Bei etwa der Hälfte aller in deutschen Apotheken verkauften Packungen handelt es sich um rezeptfreie Arzneimittel, sogenannte ‚OTC‘-Präparate. Deren Gebrauch und Regulierung haben somit eine sehr hohe Public-Health-Relevanz. Dennoch wird OTC-Arzneimitteln in der pharmakologischen und arzneimittelregulatorischen Literatur nur eine sehr eingeschränkte Aufmerksamkeit gewidmet. Auch ist nur wenig empirische Evidenz zum Gebrauch von OTC-Arzneimitteln und zur Risikowahrnehmung bezüglich OTC-Arzneimitteln verfügbar.

Umfang: Die vorliegende Dissertation basiert auf vier wissenschaftlichen Einzelarbeiten. Diese befassen sich mit der Wahrnehmung und dem Verbraucherverhalten im Zusammenhang mit OTC-Arzneimitteln, mit den Gründen für fruchtlose Anträge auf Änderungen der Verkaufsabgrenzung von Arzneimitteln, mit pharmakologischen Perspektiven bei sogenannten ‚Rx-to-OTC Switches‘, also Änderungen der Verkaufsabgrenzung von verschreibungspflichtigen (Rx) zu rezeptfreien (OTC) Arzneimitteln und mit der Prävalenz und den Prädiktoren der Verwendung von OTC-Präparaten bei den in Deutschland lebenden Erwachsenen.

Methoden: Ansatz dieser Arbeit sind verschiedene Forschungsmethoden. Sie umfasst eine Online-Umfrage, qualitative Inhaltsanalysen und eine epidemiologische Analyse von Daten aus der ersten Phase der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1).

Ergebnisse: Die 7-Tage-Prävalenz der Nutzung von OTC-Produkten durch die in Deutschland lebenden Erwachsenen beträgt 40,2%. Weibliches Geschlecht, fortgeschrittenes Alter, reduzierter subjektiver Gesundheitszustand und Multimorbidität waren signifikante Prädiktoren für die Verwendung von OTC-Arzneimitteln. Zwischen 2006 und 2015 gab es sieben Rx-to-OTC Switches, aber nicht alle dieser Entscheidungen waren vollständig konform mit den Empfehlungen des EU-Leifadens zu Verkaufsabgrenzungsänderungen im Arzneimittelhandel. Auch sonst waren negativ beschiedene oder ergebnislose Anträge auf Rx-to-OTC Switches, OTC-to-Rx Switches und auf sonstige Änderungen der Verkaufsabgrenzung nicht selten. Auf Expertenebene waren die häufigsten Gründe für abgelehnte Anträge Sicherheitsbelange bei den Arzneimitteln und eine unzureichende Datenlage.

Auf Politikebene wurden die abschlägigen Entscheidungen hauptsächlich aufgrund rechtlicher Beschränkungen getroffen. Außerdem wurde im Rahmen dieser Dissertation festgestellt, dass die Risikowahrnehmung bei OTC-Präparaten weitgehend vom Verabreichungsweg abhängt und davon, ob es sich bei den Produkten um pflanzliche Präparate handelt. Darüber hinaus werden nicht immer alle Einzelheiten auf dem Beipackzettel von Verbrauchern gelesen. **Fazit:** Diese Dissertation stellt die erste Messung zur OTC-Arzneimittelanwendung in einer repräsentativen Stichprobe der in Deutschland lebenden erwachsenen Bevölkerung dar. Mit einer 7-Tage-Prävalenz von 40,2% ist der Konsum von OTC-Produkten signifikant. Während die Anträge auf Änderungen der Verkaufsabgrenzung und deren weiterer Verlauf transparent sind, lassen sich die Gründe für negative Empfehlungen weit weniger gut nachvollziehen. Auf der Grundlage der Ergebnisse der vorliegenden Arbeit konnte eine Reihe von Vorschlägen für die Verbesserung der Regulierung von OTC-Arzneimitteln in Deutschland formuliert werden. Das BfArM und der Bundesrat sollten detaillierte Begründungen für negative Entscheidungen bei den Anträgen auf Änderung der Verkaufsabgrenzung liefern. Bereits verfügbare Daten, zum Beispiel aus umfassenden epidemiologischen Studien, lassen sich nutzen, um die Entscheidungsfindung hinsichtlich potentieller Änderungen der Verkaufsabgrenzung von Arzneimitteln zu unterstützen. Diese Studien sollten Selbstmedikation und die Verwendung von OTC-Präparaten voneinander unterscheiden; außerdem sollten sie Informationen zu Dosierung und Dauer der OTC-Arzneimittelanwendung sammeln. In der Vergangenheit vorgenommene Verkaufsabgrenzungsänderungen sollten evaluiert werden, so dass die gewonnenen Erkenntnisse als Informationsgrundlage für künftige Entscheidungen dienen können. Außerdem wird empfohlen, dass das BfArM und der Sachverständigenausschuss für Verschreibungspflicht einen Kriterienkatalog erarbeiten, der sowohl die Risiken als auch die Vorteile der OTC-Verfügbarkeit von Arzneimitteln berücksichtigt. Dieser könnte wiederum als Struktur für die Beratungen des Sachverständigenausschusses für Verschreibungspflicht dienen, aber auch zur systematischeren und transparenteren Dokumentation der Ausschusssitzungen. Darüber hinaus könnte die Erarbeitung eines solchen Kriterienkataloges zusätzlichen Forschungsbedarf identifizieren, um die Evidenzgrundlage der OTC-Arzneimittelregulierung zu verbessern.

12. ANNEXES

Annex I

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Barrenberg E, Garbe E

Use of over-the-counter (OTC) drugs and perceptions of OTC drug safety among German adults

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Abstract

Purpose: In Europe, little empirical evidence is available about OTC drug consumption and risk perceptions. The objective of this study was to describe consumers' OTC drug use and perceptions of OTC drug safety in Germany.

Methods: An online survey based on a quota sample with combined strata for age, gender, and education of 300 adult German participants was conducted in June and July 2013. The survey questionnaire covered participants' OTC and prescription drug use, risk perceptions of OTC and prescription drugs, package leaflet reading habits, and OTC drug off-label use.

Results: 7-day prevalences of OTC drug use were higher in women (52.0%) than in men (40.8%). The risk perception of specific OTC drugs was impacted by the route of administration, the indication, and the drugs' ingredients. Products for dermal application or plant-based products were considered 'rather not risky' by more than 80% of the participants. Products for oral use or chemically synthesized substances were considered less safe. While 48.0% of consumers reported always reading the package leaflet of OTC drugs, 44.5% reported not reading it if they knew the drug or believed the drug was very safe. People, 60 years and older, reported significantly lower levels of OTC drug off-label use (9.3%) than younger people (22.0%).

Conclusions: The 7-day prevalence of OTC drug use in Germany is high, especially among women. Consumers generally have balanced perceptions regarding OTC drug safety. Behaviours and knowledge related to OTC drug use should be considered by health care providers and regulators.

Key words: Nonprescription drugs, OTC drugs, risk perception, survey

Introduction

Over the last decades, numerous drugs have been switched from prescription only to over-the-counter (OTC) status in Europe [1]. While this development permits more patient autonomy, contributes to higher appreciation of pharmacists' knowledge and puts less fiscal pressure on European publicly funded healthcare systems [2], concerns about misuse and abuse of OTC drugs have been expressed in the German scientific [3] as well as the popular media [4, 5]. Nonetheless, use of OTC drugs is substantially understudied in German drug utilization research. OTC drug consumption is not covered by routinely collected health insurance data which are otherwise often used to study drug utilization and drug safety. Little is known empirically on how the increased availability of OTC drugs is reflected in German consumers' perceptions and behaviours regarding OTC drugs.

Several studies have estimated the one- or four-week period prevalence of OTC drug consumption among German adults during the last three decades, ranging between 13.1% and 38.5% [6-8]. More recent studies also investigated specific knowledge and risk awareness of OTC drugs among adults in England [9], Italy [10], the Netherlands [11], and Northern Ireland [12]. In Germany, similar studies among adults are lacking so far. In 2000, a pilot survey among Dresden adolescents studying their basic knowledge of self-medication found that knowledge was acquired through drug intake and not before starting drug consumption [13]. Additionally, the prevalence of prescription and OTC drug use and possible factors predisposing to their off-label use in the German paediatric population were researched most recently [14]. The aim of the present study was to broaden the European evidence base on consumers' perceptions and behaviours regarding OTC drugs among adults in Germany.

Methods

An online survey questionnaire on OTC drug use, risk perception of OTC and prescription drugs, package leaflet reading habits, and off-label use was developed by the authors. In April 2013, it was pre-tested in 17 adult male and female participants covering the age groups 18-29 years, 30-59 years, and 60 years and older as well as the educational groups basic school education, intermediate education and higher education. After adjustments to the questionnaire based on pre-testers' feedback, the survey was conducted in June and July 2013 using an online access panel. The panel relies on a cash incentive programme and comprises 250,000 panellists with a validated German address recruited actively and passively through online and offline methods [15]. A random sample of 4106 panellists was invited in two stages: Initially, a group of 486 panellists was invited. After 47 responses, the answers were checked to identify a possible lack of clarity within the questions, and it was decided that no further amendments to the questionnaire were necessary at that stage. Subsequently, 3620 panellists were invited aiming at a total sample size of $n = 300$ survey participants. In order to achieve a minimum level of representation of different age, gender and educational groups within the sample, quotas were introduced. Two gender (male and female), seven age (18-24, 25-29, 30-39, 40-49, 50-59, 60-64, and ≥ 65 years), and three educational (school degrees, graduated from vocational training, and tertiary education) were combined into 42 quotas, in addition to one quota for miscellaneous educational degrees across all age and gender categories. A maximum number of participants was defined for each quota – weighted on the basis of demographic characteristics of the general German population. Twelve days after the survey launch, a reminder was sent to 1600 panellists.

The survey questionnaire consisted of 22 questions. The questions covered the participants' socio-demographic background and their last OTC drug and prescription only medicine (POM) use

according to the time intervals 'in the last seven days, including today', 'in the last three months', 'more than three months ago', and 'never' and included the names of the last and ever used drugs. Participants were also asked to rate the frequency of their OTC drug use according to the categories 'chronic', 'frequent', 'occasionally', 'rare', and 'never' and to indicate what OTC drug safety meant to them. Regarding the latter, participants could select multiple answers covering several aspects of drug safety such as probability of side effects and risk-benefit ratio but also answers regarding drug quality and efficacy. Subsequently, participants were asked to rank their perception of OTC drug and POM safety, respectively, on a scale ranging from 1 to 9 with 1 representing 'not safe at all' and 9 representing 'extraordinarily safe'. Participants were further asked to judge 14 different OTC products as 'rather risky' or 'rather not risky' based on a list of the 20 most commonly sold OTC drugs in Germany. The 14 OTC products in the questionnaire were described in terms of indication and active ingredients to improve understanding, especially if participants were not familiar with the product in question. Simple language with words of German rather than of Latin or Greek origin was used in the descriptions and acetylsalicylic acid (ASA) was referred to as 'aspirin®' to better reflect spoken language. The possibility to skip the question was granted in case participants did not feel comfortable in judging the substances if they were unfamiliar with them. Furthermore, participants were asked whether they read the package leaflet of OTC drugs and POM, and –if applicable– to state reasons for not reading the OTC drug package leaflet at all or to indicate which information in the leaflet they would read. Participants were also asked if they had ever used OTC drugs not in line with the instructions on the package leaflet in terms of dose, duration of use, and indication ('off-label use'). Due care was taken to complement multiple-choice questions with open-ended answer options to allow for diversification of responses [16]. In a final open-ended question, participants could convey further thoughts regarding OTC drug safety. The original questionnaire in German can be found in the supplementary materials.

Chi-square tests were used to analyse categorical data. Binomial tests were used to analyse responses to dichotomous questions. Correlations were calculated according to Pearson. Student's t-test and ANOVA were used to study inferences where the dependent variables were normally distributed. Cronbach's α was calculated to evaluate internal consistency of the participants' responses indicating specific POM or OTC drug use in the different time intervals before the survey with participants' answers regarding their ever use of POM or OTC drugs. All statistical tests were two-sided. A p-value of < 0.05 was considered indicative of statistical significance. All statistical analyses were conducted with SPSS 21.

Results

Sample characteristics

The overall response rate was 24.5% (1006 out of 4106); 634 respondents were not admitted to participate due to full quotas and 72 incomplete questionnaires were excluded from analysis.

Out of 300 study participants, 50.7% were male and 49.3% were female. The mean age was 48.3 (SD 16.8) years. For the highest educational degrees obtained, 25% reported school education, 51.3% completed vocational education and 23.7% completed tertiary education.

Table 1: Demographic characteristics of survey participants

Demographic characteristics of survey participants (n = 300)			
		n	%
Gender (n = 300)	Female	148	49.3
	Male	152	50.7
Age in years (n = 300)	18-29	55	18.3
	30-39	43	14.3
	40-49	59	19.7
	50-59	53	17.7
	60-69	57	19.0
	70-79	26	8.7
	80-85	7	2.3
Education (n = 300)	Basic school education	17	5.7
	Secondary school education	31	10.3
	High school education	27	9.0
	Vocational training	154	51.3
	Tertiary education (incl. master craftsman "Meister" and certified engineer "Techniker" or equivalent)	71	23.7
Health profession / work experience in a health care setting	Yes	48	16.0
	No	252	84.0

Reporting of OTC drug use and internal consistency

Table 2: Reported recency of last OTC drug and POM use

	All participants (n = 300)	Females (n = 148)	Males (n = 152)
OTC drugs			
Last seven days	139 (46.3%)	77 (52.0%)	62 (40.8%)
Three months to last seven days	102 (34.0%)	45 (30.4%)	57 (37.5%)
Prior to last three months	51 (17.0%)	24 (16.2%)	27 (17.8%)
Never	8 (2.7%)	2 (1.4%)	6 (3.8%)
POM			
Last seven days	144 (48.0%)	74 (50%)	70 (46.1%)
Three months to last seven days	84 (28.0%)	46 (31.1%)	38 (25.0%)
Prior to last three months	68 (22.7%)	27 (18.2%)	41 (27.0%)
Never	4 (1.3%)	1 (0.7%)	3 (2.0%)

The reported recency of the last OTC drug and POM use by participants is presented in table 2. Reported OTC drug use in the last 7 days was with 46.3% very common, and similar to POM use in the same time span.

Rating the frequency of their OTC drug use, 11.1% considered themselves chronic users, 13.5% frequent users, 47.6% occasional users, 26.3% rare users, and 1.4% never users. There was a weak, statistically significant correlation between recency of reported last OTC drug and POM drug use ($r = 0.425$, $p < 0.001$). No statistically significant correlation was found between age and recency of reported last OTC drug use, but a weak correlation was observed between age and reported last POM use ($r = 0.208$, $p < 0.001$), implying that POM use increases with age. No statistically significant correlation was found between different educational levels and reported last OTC drug use nor between education and self-classification of OTC drug use frequencies.

The internal consistency was assessed on the basis of the reported last OTC drug and POM use, showing a Cronbach's α of 0.8.

OTC drug risk perception

While 5.3% of study participants considered OTC drugs 'extraordinarily safe' corresponding to a value of 9 on a scale from 1 to 9, the mean perceived safety of OTC drugs was 6.1 (SD 1.8). The perceived safety of POM was with 6.8 (SD 2.0) higher than that of OTC drugs ($p < 0.001$). There was a strong correlation between the perception of OTC drug and POM safety ($r = 0.657$, $p < 0.001$).

The perception of OTC drug safety did not correlate with the recency of OTC drug use. The mean perceived safety of OTC drugs of 3.0 among those reporting having never used OTC drugs was statistically significantly lower ($p = 0.007$) than the mean of 6.1 among those reporting having ever used OTC drugs. Perceived OTC drug safety did not differ by gender, educational group or between people who had a health-related profession / work experience in a health care setting or not. With a mean of 5.6 of perceived OTC drug safety, participants who were 60 years or older reported statistically significantly lower levels ($p = 0.022$) than those who were younger where the mean was 6.2.

In rating the perceived safety of specific OTC products, drugs for dermal application (cream containing dexpanthenol and diclofenac diethylamine gel), plant-based products (Sinupret® dragées, GeloMyrtol® capsules and Iberogast® drops) or lozenges containing cetylpyridinium chloride 1H₂O and benzocaine were rated as 'rather not risky' by more than 80% of the survey participants. Analgesics for oral use (paracetamol, ASA, ibuprofen), including combination products and nasal decongestant spray containing xylometazoline were considered as 'rather not risky' by 50-70% of the participants. Tablets containing 100 mg ASA formed an exception as they were considered 'rather not risky' by only 36.1% of the respondents. The difference of proportions between the answers 'rather risky' and 'rather not risky' was found to be statistically significant ($p < 0.05$) for all but three OTC products in question (see supplementary materials).

Participants who mentioned having used a certain OTC drug in the past were in general more likely to judge the respective drug as 'rather not risky' than those who had not mentioned using it previously. This observation was statistically significant ($p < 0.05$) for nasal decongestant spray containing xylometazoline, 100 mg ASA tablets, and ibuprofen. In general, the survey participants displayed a broad range of knowledge regarding possible routes of administration of POM and OTC drug substances including tablets, capsules, ointments, gels, drops, creams, granules, syrups, suspensions for injection, patches, sprays, suppositories, effervescent tablets, and lozenges. However, occasionally the participants additionally mentioned products different from OTC drugs, such as medical devices, food supplements, freely-sold medicines, homeopathic preparations, cosmetics as well as liquorice and cough sweets.

Regarding the multiple-select question about what OTC drug safety meant to the participants, the most common replies were 'effectiveness when used for the right reason' ($n = 152$), 'low probability of side effects when used correctly' ($n = 125$), 'risks and benefits of drug use are proportionate' ($n = 122$), and 'material purity of the drugs' components' ($n = 120$). The response 'no side effects when used correctly' was selected by 82 respondents.

Twenty-five participants answered the open-ended question about other thoughts on OTC drug safety. Several mentioned being interested in and the relevance of the topic and found the survey helpful to reflect their own OTC drug use and attitudes. Additionally, there were a number of comments regarding herbal medicines, internet sales of drugs, psychological effects related to drug use, experiences with adverse drug reactions, and concerns about ‘old’ or ‘young’ people or relatives using too many OTC drugs.

Consumer behaviours with respect to reading the package leaflet

Among the survey participants, 144 (48.0%) reported always reading the package leaflet of OTC drugs, 17 (5.7%) reported never reading it and 139 (46.3%) reported that ‘it depends’ whether they read it or not. Of the latter, 110 (79.1%) reported not reading the package leaflet if they knew the medication, 7 (5.0%) reported not reading it if they considered the medication ‘very safe’, 17 (12.2%) reported not reading it if both of these were true and 5 (3.6%) reported other reasons. The package leaflet of POM was always read by 145 (48.3%) survey participants and never by 11 (3.7%). The answer ‘it depends’ was chosen by 144 (48.0%) respondents. There was a significant correlation between reading the package leaflet of POM and OTC drugs ($r = 0.533, p < 0.001$). Among those who read the OTC package leaflet always or under certain conditions, information on dosage was read most often. Among those who reported never reading the OTC package leaflet ($n = 17$), the most frequently cited reason was ‘advice from the pharmacy is sufficient for me’ ($n = 9$).

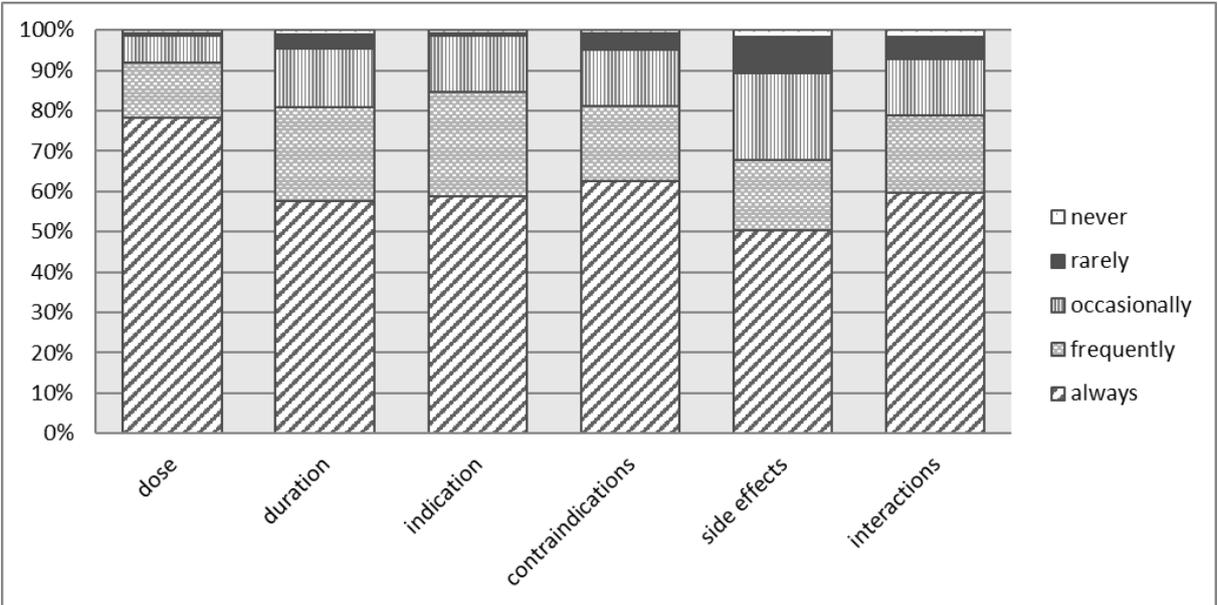


Fig. 1: Information read in the package leaflet of OTC drugs by those claiming to always or under certain conditions read the package leaflet

OTC drug off-label use

Of all survey participants, 53 (17.7%) reported having ever used OTC drugs off-label. Off-label use was reported by 30 (20.5%) females and 23 (15.9%) males. The gender difference was not statistically significant. Regarding age, however, 45 (22.0%) people below 60 years of age reported OTC drug off-label use while only 8 (9.3%) of those being 60 years and older stated having used an OTC drug off-label previously. This difference was statistically significant ($p = 0.022$). There was no statistically significant association between OTC drug risk perception and OTC drug off-label use.

Discussion

This study found a 7-day OTC drug use prevalence of 46.3% among German adults. Their risk perception was influenced by the route of administration, the drug's indication and the active substance: Plant-based products and those for dermal application and lozenges were considered having the lowest risk, analgesics were considered of medium risk, and ASA used as anticoagulant was associated with the highest risk. Risk perception was lower in participants with a previous use of a given OTC drug. Only 5% of the study participants reported never reading the package leaflet of OTC drugs. Among those reporting reading the OTC package leaflet always or only certain parts of it, dose, indication, and contraindications were the most frequently read aspects, while side effects received less attention.

The 7-day prevalence of 46.3% of OTC drug use found in this study was higher than findings from previous studies: The 2009 telephone health survey in North Rhine-Westphalia reported a four-week period prevalence of 38.5% of OTC drug consumption [6]. The representative German National Health Interview and Examination Survey included 7099 participants aged 18-79 in its Drug Utilization Survey 1998. In a face-to-face interview, the survey found a 7-day prevalence of 35.1% of self-medication and higher rates in women (40.1%) than men (29.9%) [7]. In 1990, data from the study site Augsburg of the MONICA study reported 9.8% of men and 16.5% of women aged 30-64 years using non-prescription drugs during the 7 days prior to the face-to-face interview [8]. Although different methods were used in the respective studies, e.g. telephone and online surveys versus face-to-face interviews, and the studies included different age groups, there seems to be an increase in OTC drug use over time. This may be explained by the better availability of OTC drugs in recent years – research conducted for the European Commission found that about 60 active ingredients had been made available for OTC sales between 2002 and 2012 [17] – higher acceptability, and higher need or higher perceived need for OTC drugs over time. Hanna and Hughes found that many consumers were willing to buy OTC drugs regardless of the evidence of their effectiveness [18]. Another possible explanation for the higher OTC drug use in our study compared to previous ones might be that

reporting of such use is higher in online surveys due to the higher anonymity as compared to telephone surveys or large epidemiological field studies with face-to-face interviews. On the other hand, the high prevalence might also be due to over-reporting: When the survey participants were asked about recently or formerly consumed medication, they also mentioned medicinal or other products that can be obtained in pharmacies for which a differentiation from OTC drugs can be difficult to make even for experts.

The finding of women using more OTC drugs than men was in line with previous research findings from Germany [7, 8] as well as from other countries [19-23]. Women's higher use of analgesics can partially be explained by different pain perception and menstrual pain [24]. Other possible explanations include a higher health awareness of women, their generally higher use of health services and better knowledge about pharmaceuticals among women [7] and girls [13].

This study could not find an association between OTC drug use and educational status, while Mensing, Streich & Terschüren [6] found that OTC drug use was lower for the lowest social strata in North Rhine-Westphalia compared to middle and upper social strata. This discrepancy can possibly be explained by recognising that the socio-economic status is usually derived from both education and income and that the latter may be the single factor explaining differences in OTC drug consumption. This phenomenon is also reflected in public health practice in terms of the so-called 'medication banks' [Medikamententafeln] where people living in economically difficult situations are provided with 25-80% discounts on OTC drugs in some German regions [25, 26].

Furthermore, this research has shown a balanced attitude on OTC drug safety among German consumers. With a mean of 6.05, the participants considered OTC drugs as generally safe, but did not regard them as products without any risk; a finding also made by Krska et al. in a study population from Liverpool [9]. Our result of only 5.3% of participants judging OTC drugs as 'extraordinarily safe' diverges from that of the Northern Irish study by Wazaify et al. which found that about half of the participants agreed that OTC drugs were 'totally safe' [2]. However, in the same study more than 60% of the participants also agreed that OTC drugs 'can have dangerous side-effects' [2], which underlines a balanced attitude on OTC drug safety. It should also be mentioned that in the United Kingdom of Great Britain and Northern Ireland, products containing codeine are available OTC [2], which is not the case in Germany. The participants of the Northern Irish study identified these products as being particularly prone to abuse [2].

A 2008 study focusing on OTC drug risk perception among Italian consumers found that the risk awareness of OTC drugs is generally high [10]. Nonetheless, our study showed a strong difference in

risk perception regarding different OTC drugs with a relatively low risk perception for drugs with dermal application, followed by lozenges, and plant-based products. It is well known that plant-based products may lead to dangerous herb-drug [27, 28] or drug-drug interactions. For example, St John's wort reduces the bioavailability of immunosuppressant drugs thereby increasing the risk of organ rejection in transplantation patients [29]. While all of the plant-based products enquired about in this study have a favourable safety profile, our results could yet indicate a possible misconception of the safety of plant-based OTC drugs with harmful interactions. It is also known that notions like 'natural' are generally associated with lower risk perception [30]. Patients should be educated in this respect by pharmacists and other health care workers.

The fact that participants rated OTC drugs as somewhat more risky than POM was an unexpected finding: One of the criteria for a regulatory switch of a medicine from prescription to OTC status is the fact that this drug is overall considered safe [31]. It is highly likely that the survey participants were not aware of this prerequisite – to our knowledge; there is no public awareness campaign on the issue of drug safety in relation to switches in prescription status. The finding may also be explained by methodological issues: In the survey questionnaire, OTC drugs were defined as 'drugs that can be bought in a pharmacy without a prescription' and POM as 'drugs that require a prescription from a physician'. These definitions may have caused respondents to consider OTC drugs and POM administered in outpatient settings only, thereby disregarding drugs administered in hospital with a less favourable safety profile, as, e.g. cancer chemotherapy. However, this finding is in line with results from a British survey where OTC drugs were more often perceived as less safe than POM [9]. The present study did not find a correlation between risk perception and OTC drug off-label use. This can possibly be explained by too little statistical power as the reported off-label use was low. The finding differs from a US-American study which observed more off-label use in people with a low risk perception of OTC drugs [32].

This study has shown that the package leaflet is often not read if consumers know the OTC drug already and that not all aspects of the package leaflet receive equal attention. While dose, indication, and contraindications are the most read aspects of the package leaflet, duration and interactions receive less attention, and side effects are the least read aspect. A possible explanation is that knowledge about side effects is not required for the immediate safe use of OTC drugs and this section of the package leaflet is not read unless potential side effects occur. Similarly, information on interactions is only relevant to those who use other drugs at the same time and information on duration may only become relevant if consumers consider prolonged use. It may be advisable for drug regulatory authorities to factor the extent to which certain aspects of the package leaflet are read by consumers into their decisions, in particular regarding switches from prescription to OTC

status. Also, health care workers should raise patients' awareness of OTC drugs' possible interactions and side effects where relevant. Our findings complement the results of an Italian study by Calamusa et. al. which studied the ability of consumers to understand package leaflets. While 70.7% of their respondents cited the package leaflet as a source of information, only 38.1% claimed to completely understand its contents. About 40% of the participants were unable to make a simple calculation determining the correct maximum daily dose [10].

Our survey participants showed generally a good understanding of the definition of drug safety, although many also named other criteria for market admissibility such as 'effectiveness when used for the right reason' conforming to similar findings made by Krska et al. [9]. Only one sixth of the participants believed that no side effects can be expected when an OTC drug is used correctly.

This study has several limitations. Firstly, a certain level of selection bias cannot be excluded. The online study panel relies on a cash-incentive programme [15] which is known to enhance representativeness through increased response rates [33]. Nonetheless, the non-response level of 75.5% was relatively high. It is a common phenomenon that people who have a strong interest in the subject matter or wish to contribute to the advancement of science are more likely to participate in online surveys [34]. Because the study was an online survey it is unlikely to have included people without an internet connection or with low computer literacy. It is conceivable that people without a computer or internet connection have different perceptions of OTC drugs, as they may have generally negative perceptions of innovation and technology. However, in Germany, 75.6% of the population had internet access in 2012 [35], so the group of people not being online is relatively small. Also, we tried to account for differences in internet use among various age, gender, and educational groups through combined quotas. Secondly, the survey questionnaire has not been validated. At the moment, no validated instrument is available for this type of research, but there were good levels of internal consistency with Cronbach's α of 0.8 for the assessed items. Thirdly, the prevalence estimate relied on self-reporting which cannot be validated in the context of online surveys. However, when studying OTC drug use, not many options beyond self-reporting are available. While face-to-face studies can rely on the brown-bag method which is thought to increase comprehensiveness and accuracy of the reported use [36, 37], this is not possible in the context of online-surveys. Fourthly, survey research cannot be used to draw causal relationships [38]. Nonetheless, this study adds to the scarce evidence of OTC drug utilization research and perceptions of OTC drug safety in Germany.

Conclusions

This study found a relatively high 7-day prevalence of self-reported OTC drug use in the German adult population and balanced consumers' views on the risks related to OTC drugs. Our findings contradict

German popular media reports which claim that consumers use OTC drugs too carelessly and are unaware of the potential associated risks. Although there were no strong patterns observed regarding age, gender or educational groups regarding attitudes and behaviours concerning OTC drug use and risk perception, this study has provided a number of useful starting points for public health interventions. For example, pharmacists and other health care workers should address possible misconceptions regarding the safety of plant-based OTC drugs with their patients. Further research is necessary to study how consumers can be best supported in using OTC drugs safely and how social and behavioural dimensions of OTC drug safety can be better reflected in regulatory decisions.

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Conflict of Interest: The study did not receive any external funding. EB has no conflict of interest. EG is running a department that occasionally performs studies for pharmaceutical industries. These companies include Bayer, Celgene, GSK, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA. EG has been a consultant to Bayer, Nycomed, Teva, GSK, Schwabe and Novartis.

Contributions of authors statement: EB and EG conceptualized the study. EB conducted the data analysis and prepared the manuscript, EG provided substantive intellectual input and critically reviewed the manuscript.

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Supplementary materials of annex I

Table: Risk perception of 14 different OTC products

OTC drug	% of survey participants classifying the drug as 'rather not risky'
Cream containing dexpanthenol (Bepanthen® Wund- und Heilsalbe) used for minor wounds and mucosal irritations*	96.6
Diclofenac diethylamine gel (Voltaren® Schmerzgel) used for joint pain and sports injuries*	88.6
Coated tablets containing a plant-based preparation (Sinupret® Dragees) used for inflammation of the sinuses*	85.6
Lozenges containing cetylpyridinium chloride 1H ₂ O and benzocaine (Dobendan Strepsils®) used for inflammations of mouth and throat*	84.7
Capsules containing plant-based distillates (GeloMyrtol® Kapseln) used for dissolving mucus during cough and colds*	84.5
Drops containing a plant-based herbal preparation (Iberogast® Tropfen) used for gastrointestinal problems*	82.7
Capsules containing paracetamol, caffeine and vitamin C (Grippostad® C) used for colds and fever*	68.8
Tablets containing paracetamol 500 mg used for pain and fever*	63.2
Tablets containing ASA 500 mg used as painkiller*	59.7
Nasal decongestant spray containing xylometazoline used for nasal congestion*	57.7
Powder for suspension preparation containing 500 mg ASA and pseudoephedrine hydrochloride (Aspirin® Complex) used for flu-like symptoms	55.4
Ibuprofen 400 mg used as painkiller	54.7
Tablets containing different active ingredients and caffeine (Thomapyrin®) used as painkiller	54.4
Tablets containing 100 mg ASA used as anticoagulant*	36.1
* The difference between 'rather risky' and 'rather not risky' was statistically significant at $p < 0.05$ level.	

Survey

Wahrnehmung von Arzneimittelsicherheit bei rezeptfreien Arzneimitteln

1. Sind Sie weiblich oder männlich? (eine Antwort möglich) (Pflichtfrage)

Weiblich

Männlich

2. Wie alt sind Sie? (Pflichtfrage)

<freifeld> Jahre

3. Was ist ihr höchster Bildungsabschluss? (eine Antwort möglich) (Pflichtfrage)

Grund-/Volks-/Hauptschulabschluss

Realschulabschluss, Abschluss der Polytechnischen Oberschule, oder gleichwertig

Fachhochschulreife/ Allgemeine Hochschulreife

Abgeschlossene Berufsausbildung → zu Frage 4

Meister/ Techniker

Fachhochschulabschluss

Hochschulabschluss

>freifeld<

4. (nur Anzeigen, wenn Frage 3 mit „Abgeschlossene Berufsausbildung“ beantwortet wurde)
Welche Berufsausbildung haben Sie?

>freifeld<

5. Wann haben Sie zuletzt **rezeptfreie** Arzneimittel, also solche, die man in der Apotheke ohne Rezept kaufen kann, benutzt? (Pflichtfrage)

In den letzten 7 Tagen einschließlich heute

In den letzten 3 Monaten

Vor mehr als 3 Monaten

Noch nie

6. Wann haben Sie zuletzt **rezeptpflichtige** Medikamente, also solche, für die man ein Rezept vom Arzt benötigt, benutzt? (Pflichtfrage)

In den letzten 7 Tagen einschließlich heute

In den letzten 3 Monaten

Vor mehr als 3 Monaten

Noch nie

7. (nur anzeigen, wenn Frage 5 und 6 nicht beide mit „noch nie“ beantwortet wurden) Welches Produkt haben Sie zuletzt gebraucht (rezeptfrei und/oder rezeptpflichtig)?
<freifeld>
8. (nur anzeigen, wenn Frage 5 und 6 nicht beide mit „noch nie“ beantwortet wurden) Können Sie sich darüber hinaus an den Gebrauch weiterer Produkte erinnern (rezeptfrei und/oder rezeptpflichtig)?
<freifeld>
9. Wie würden Sie die Häufigkeit Ihres Arzneimittelgebrauchs selbst einordnen? (nicht anzeigen, wenn Fragen 5 und 6 beide mit „nie“ beantwortet wurden)

Häufigkeit der Einnahme **rezeptfreier** Arzneimittel
chronisch – häufig – gelegentlich – selten – nie

Häufigkeit der Einnahme **rezeptpflichtiger** Arzneimittel
chronisch – häufig – gelegentlich – selten – nie

10. Was verstehen Sie unter Arzneimittelsicherheit bei **rezeptfreien** Arzneimitteln?
(Mehrfachnennung möglich) (Pflichtfrage)
Hinweis: Mehrfachantworten möglich

Keine Nebenwirkungen bei korrekter Einnahme

Geringe Wahrscheinlichkeit von Nebenwirkungen bei korrekter Einnahme

Keine Nebenwirkungen bei leichten Abweichungen von korrekter Einnahme

Geringe Wahrscheinlichkeit von Nebenwirkungen bei leichten Abweichungen von korrekter Einnahme

Wirksamkeit bei Einnahme aus dem richtigen Grund

Stoffliche Reinheit der Bestandteile des Arzneimittels

Nutzen und Risiko des Arzneimittelgebrauchs stehen in einem angemessenen Verhältnis

<freifeld>

11. Für wie sicher halten Sie rezeptfreie bzw. rezeptpflichtige Arzneimittel?
>Jeweils Polaritätenprofil gar nicht sicher – außerordentlich sicher, 9 Abstufungen, Spalte „nicht beantwortbar“<
- Rezeptfrei
 - Rezeptpflichtig

12. Für wie risikobehaftet halten Sie die folgenden Produkte?

Produkt	Eher risikoarm	Eher risikoreich
Paracetamol 500mg (Schmerz- und Fiebermittel)		
Nasenspray gegen Erkältungen (Wirkstoff: Xylometazolin)		
Thomapyrin® (Schmerzmittel, Kombination aus verschiedenen Wirkstoffen und Koffein)		
Grippostad® C (gegen Erkältungen und Fieber; Wirkstoff: Paracetamol, Vitamin C und Koffein)		
Voltaren® Schmerzgel (gegen Gelenkschmerzen und bei Sportverletzungen, Wirkstoff: Diclofenac-Natrium)		
Sinupret® Dragees (pflanzliches Produkt gegen Nasennebenhöhlenentzündungen)		
TAH Tabletten (Blutverdünner, Wirkstoff Aspirin® 100mg)		
Bepanthen® Wund- und Heilsalbe (gegen leichte Haut- und Schleimhautschäden, Wirkstoff: Dexpanthenol)		
Ibuprofen 400mg (Schmerzmittel)		
GeloMyrtol® Kapseln (pflanzliches Produkt, Schleimlöser bei Husten und Schnupfen)		
Aspirin® 500mg (Schmerzmittel)		
Iberogast Tropfen (pflanzliches Produkt gegen Magen-Darmbeschwerden)		
Dobendan Strepsils® Lutschtabletten (bei Mund- und Rachenentzündungen, Wirkstoffe: Cetylpyridiniumchlorid 1 H ₂ O und Benzocain)		
Aspirin® Complex (bei grippalem Infekt, Wirkstoffe: Aspirin® 500mg und Pseudoephedrin-Hydrochlorid)		

13. Lesen Sie die Packungsbeilage bei **rezeptpflichtigen** Arzneimitteln, also solchen, für die man ein Rezept vom Arzt benötigt?

Nie

Immer

Das kommt darauf an

14. Lesen Sie die Packungsbeilage bei **rezeptfreien** Arzneimitteln, also solchen, die man in der Apotheke ohne Rezept kaufen kann? (Pflichtfrage)

Nie → weiter Zu Frage 17

Immer → weiter zu Frage 16

Das kommt darauf an

15. Wann lesen Sie die Packungsbeilage von rezeptfreien Arzneimitteln nicht? (Mehrfachnennung möglich)

Wenn ich das Medikament kenne

Wenn ich das ich das Medikament für sehr sicher halte

<freifeld>

16. Wenn Sie eine Packungsbeilage eines rezeptfreien Arzneimittels lesen, welche Informationen lesen Sie dann darin nach?

Wie man das Medikament richtig dosiert (Dosierung)

immer –oft – gelegentlich – selten –nie

Wie lange man das Medikament maximal anwenden/einnehmen sollte (Einnahmedauer)

immer –oft – gelegentlich – selten –nie

Für welche Art von Beschwerden das Medikament gut ist (Indikationen)

immer –oft – gelegentlich – selten –nie

Wann man das Medikament nicht nehmen darf (Kontraindikationen/Gegenanzeigen)

immer –oft – gelegentlich – selten –nie

Welche Nebenwirkungen das Medikament hat (Nebenwirkungen)

immer –oft – gelegentlich – selten –nie

Ob man aufpassen muss, wenn man gleichzeitig noch andere Medikamente anwendet/einnimmt (Wechselwirkungen)

immer –oft – gelegentlich – selten –nie

17. Aus welchen Gründen lesen Sie die Packungsbeilage bei rezeptfreien Arzneimitteln nicht?
(Mehrfachantworten möglich)

<nur Anzeigen, wenn Frage 14 mit „nie“ beantwortet wurde>. (Pflichtfrage)

Die Informationen darin interessieren mich nicht

Die Informationen darin sind nicht verständlich

Die Informationen darin sind nicht hilfreich

Die Beratung in der Apotheke genügt mir

Die Informationen auf der Packung genügen mir

Die Schriftgröße ist zu klein

Die Angaben zu Nebenwirkungen verunsichern mich

<freifeld>

18. Die Sicherheit von rezeptfreien Arzneimitteln wird durch zwei Komponenten gewährleistet:

- Der Produktsicherheit, also die Qualität, Wirksamkeit und Unbedenklichkeit des Produkts
- der Arzneimitteltherapiesicherheit, also den Informationen zum richtigen Gebrauch, die auf der Verpackung, in der Packungsbeilage und durch die Beratung in der Apotheke vermittelt werden

Welchen Anteil haben diese beiden Komponenten Ihrer Ansicht nach an der Arzneimittelsicherheit von rezeptfreien Arzneimitteln?

Produktsicherheit hat den größten Anteil <Grafische Bewertungsskala „Schieberegler“ 0-100, 1-er Schritte> Arzneimitteltherapiesicherheit hat den größten Anteil

<der Schieberegler sollte von vorneherein sichtbar sein>

19. Haben Sie schon einmal **rezeptfreie** Arzneimittel in einer Weise gebraucht, die nicht den Vorgaben in der Packungsbeilage entsprach (z.B. hinsichtlich Dosierung, Einnahmedauer, Art von Beschwerden)? (nicht anzeigen, wenn Frage 5 mit „noch nie“ beantwortet wurde)

Ja

Nein

<freifeld>

20. Kennen Sie andere Personen, die schon einmal **rezeptfreie** Arzneimittel in einer Weise gebraucht haben, die nicht den Vorgaben in der Packungsbeilage entsprach (z.B. hinsichtlich Dosierung, Einnahmedauer, Art von Beschwerden)?

Ja

Nein

<freifeld>

21. Haben Sie einen gesundheitsbezogenen Beruf (oder Studium/Ausbildung/Arbeitserfahrung)?
(Pflichtfrage)

Ja

Nein

22. Haben Sie weitere Anmerkungen zum Thema dieser Befragung?
<freifeld>

Annex II

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Unsuccessful applications to increase or decrease the over-the-counter (OTC) availability of drugs in Germany between 2009 and 2014

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COMPLIANCE WITH ETHICAL STANDARDS:

Conflicts of interests: EB declares that she has no conflicts of interest. EG has served as a deputy member during one of the analysed sessions of the Expert Advisory Committee for Prescription-Only Issues.

Abstract

Aim: To provide an overview of applications to change drug prescription status submitted to the German Federal Institute for Drugs and Medical Devices between 2009 and 2014 and to examine the success of these applications based on regulatory considerations.

Methods: A content analysis of session minutes held by the Expert Advisory Committee for Prescription-Only Issues (EAC) which provides independent advice on questions of mandatory prescription to the German Ministry of Health was conducted. Additionally, changes to the Ordinance on Prescription-Only Medicinal Products were analysed.

Results: In total, there were 101 applications, 91 of which concerned non-alternative medicines for human use. The latter regarded 38 increases in over-the-counter (OTC) availability, 46 decreases in OTC availability and seven legally insignificant changes of wording. The EAC recommended rejecting 13 applications for increased OTC availability. Common reasons were substances' insufficient OTC suitability, such as inappropriate indications or the risk of delaying diagnosis of serious disease, followed by insufficient data quality of applications. Reasons for not recommending a decrease in OTC availability were that Rx status would probably not improve early detection of disease complications, that the risk of abuse of the respective OTC drug was low, and that pack size restrictions of OTC drugs may not improve patient compliance regarding restricted duration of use. These decisions also considered the public health benefits of a substance's OTC availability.

Conclusions: Insufficient data relevant to self-medication remains a common challenge for regulators. Further research on drug utilisation in the OTC setting and its implications for regulatory decisions is necessary.

Key words: OTC drugs, Rx-to-OTC switch, OTC-to-Rx switch, prescription status, regulation, Germany

Introduction

An important aspect of health protection is the adequate regulation of pharmaceuticals. Regulatory considerations regarding switches of drugs from prescription (Rx) to over-the-counter (OTC) status have been described on several occasions in the literature (Brass 2001; Gauld et al. 2012; Gauld et al. 2014; Juhl 1998). Public health motivations and implications of such switches have been subject to debate within the scientific community (Brass 2001; Gurwitz et al. 1995; Millier et al. 2013; Pawaskar and Balkrishnan 2007; Stomberg et al. 2013; Will and Weiner, 2015). Much less emphasis has been placed on applications requesting a decrease of OTC availability or on drugs switched from OTC to Rx status. At the same time, most studies and commentaries have focused on so-called *successful switches*, i.e. when a change in trade status was applied for, subsequently approved by the

regulatory agency and implemented in practice. In contrast, so-called *unsuccessful* switch applications have received rather limited attention.

Wessels (2006) provided a list of Rx-to-OTC switches in Germany between 1990 and 2000 and complemented it with a list of re-switches during the same time. Helmstaedter (1985) had compiled the same information for the years 1971-1985. Cohen (2003) compared an unsuccessful Rx-to-OTC switch application of omeprazole in the United States of America (USA) with a successful one of the same substance in Sweden. Soller et al. (2011) studied five unsuccessful first-in-class Rx-to-OTC switch applications in the USA. So far, no research is available on switch applications in Germany which have not been transposed into law. Nonetheless, regulatory decisions not in favour of applicants are inherent to the concept of regulation and of the same importance to health protection as positive outcomes.

In Germany, applications to change the prescription status of drugs have to be directed to the German Federal Institute for Drugs and Medical Devices [BfArM], which hosts the scientific secretariat to the external Expert Advisory Committee for Prescription-Only Issues (EAC). The BfArM conducts an initial assessment of each application, formulates a recommendation and presents this to the EAC. After deliberation on each application, the EAC provides a recommendation to the Federal Ministry of Health [Bundesministerium für Gesundheit, BMG]. The BMG takes the final decision in agreement with the Bundesrat (*Federal Council of Germany*). Substances with Rx-only status and exceptions thereto are listed in the annex of the Ordinance on Prescription-Only Medicinal Products [Arzneimittelverschreibungsverordnung, AmVV].

The present study reports on all applications to change drug prescription status dealt with by the German authorities between 2009 and 2014. It focuses on the direction of these changes in prescription status, expands upon unsuccessful applications in particular, and describes discussions and patterns of argumentation observed in the context of unsuccessful applications.

Materials and Methods

Scope

In Germany, there are four distinct classes of legal trade for pharmaceuticals:

1. Prescription drugs requiring special authorisation according to the German Narcotic Drugs Act [Betäubungsmittelgesetz]
2. Prescription drugs for use within health care facilities or for sale by pharmacies only
3. OTC drugs that are pharmacy-only drugs
4. OTC drugs available in pharmacies and other retail facilities

This study only considers shifts between the second and third category. For the purpose of this research, *Rx drugs* refer to the second category and *OTC drugs* to the third category. Changes in prescription status relating to the Narcotic Drugs Act or freely-sold medicines were not the subject of the analysis.

Data sources

In order to study switch applications between 2009 and 2014, the minutes of sessions 62-72 (BfArM 2009a, b, 2010a, b, 2011a, b, 2012a, b, 2013, 2014a, b) and an extraordinary session (BfArM 2011c) held by the EAC during that time period were analysed. The corresponding supporting documents, such as result reports and changes to the Ordinance on Prescription-Only Medicinal Products [Arzneimittelverschreibungsverordnung] (Bundesgesetzblatt 2009a, b, 2010, 2011a, b, 2012, 2013, 2014, 2015) were reviewed. All materials are publicly available on the homepage of the BfArM (www.bfarm.de, last accessed 25.01.2016).

Data analysis

A content analysis of the above-mentioned documents was conducted. The agenda items of the minutes were disaggregated according to the different products or active ingredients and according to the applications discussed and/or eventually put to vote for recommendation by the EAC. Homeopathic preparations and veterinary medicines were excluded.

For the purpose of the analysis, five different types of changes in prescription status were distinguished (see Table 1).

Table 1: Definitions of changes in prescription status

Category	Definition
Rx-to-OTC switch	The substance concerned was previously not available OTC. Acceptance of the application would result in OTC availability, with or without exceptions.
Increase in OTC availability	The substance concerned was already available OTC. The application sought to expand this availability in terms of higher doses, additional user groups, additional indications, other routes of administration, etc.
Decrease in OTC availability	The substance concerned was already available OTC. The application sought to decrease this availability in terms of dose, pack size, indication, etc. However, the acceptance of the application would not yet result in Rx-only status.
OTC-to-Rx switch	The substance concerned was already available OTC, with or without exceptions. Acceptance of the application would result in Rx-only status.
Legally neutral changes of wording	The application sought changes to the wording of the Ordinance on Prescription-Only Medicinal Products without changing its content, e.g. an umbrella term for a drug group was deleted in favour of introducing the name of all substances falling under it.

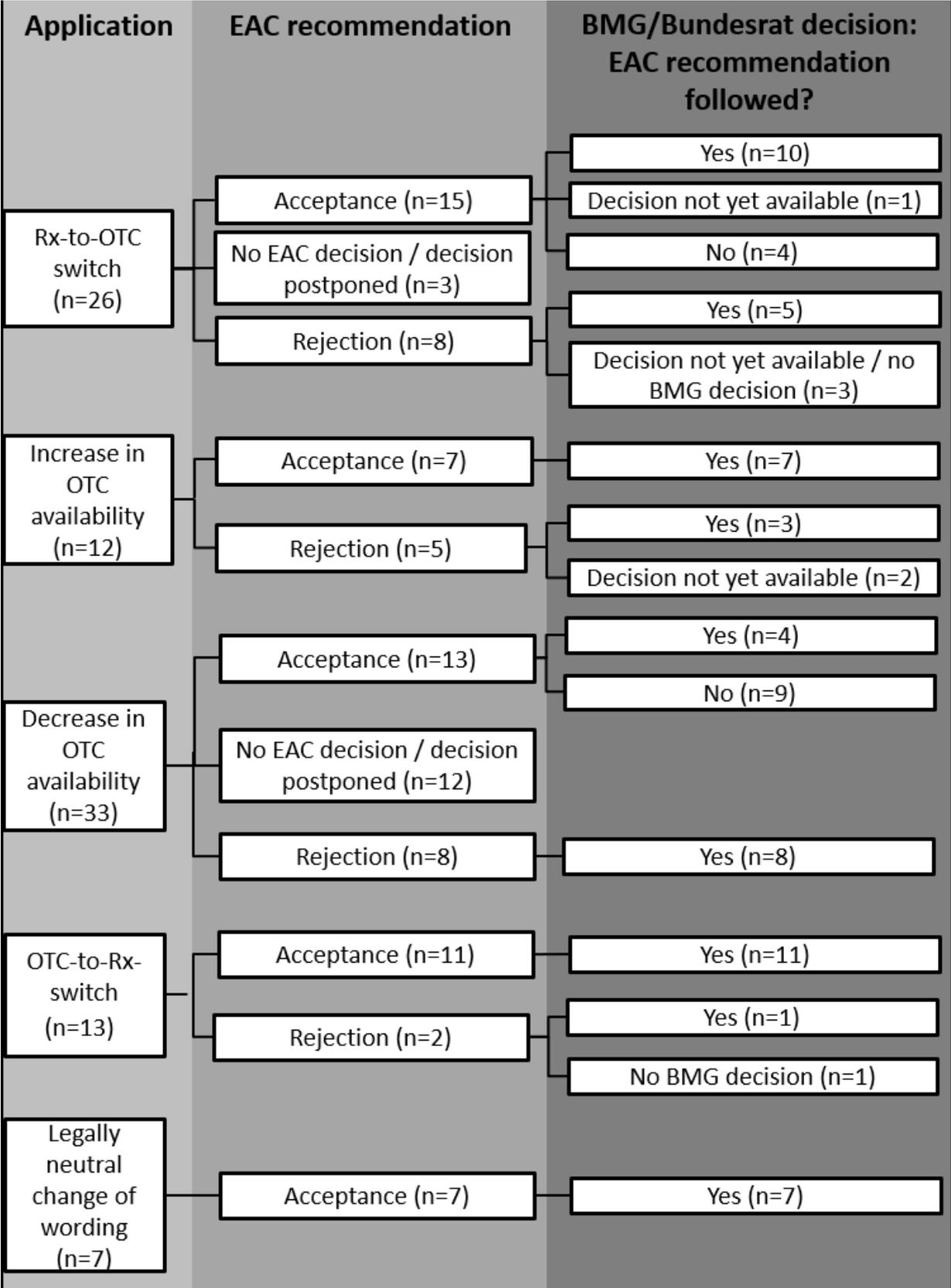
A summary of EAC discussions was available in the analysed minutes, as were the outcomes. The latter included recommendations to accept or reject the application, postponed decisions or decisions not made, e.g. if an application became redundant due to an alternative application being put forward during the same meeting.

Changes to the Ordinance on Prescription-Only Medicinal Products published between July 2009 and March 2015 were reviewed to ascertain whether the BMG and the Bundesrat had implemented the EAC recommendations. The outcome of applications was assessed as follows: If a recommendation required a change to the Ordinance on Prescription-Only Medicinal Products, the application was considered accepted at the time the legal change was gazetted. If an EAC recommendation did not require legal change but the Bundesrat could have taken a different decision, or if it was unclear whether the recommendation was followed or not, all changes to the Ordinance on Prescription-Only Medicinal Products issued after the EAC session in question and the latest consolidated version of the Ordinance on Prescription-Only Medicinal Products were reviewed in February and March 2015 with respect to the application in question. If at that point there was no evidence of legal changes, the application was considered accepted in cases where no legal change had been required and not accepted in cases where it had been unclear whether the recommendation had been followed or not. Due to the short time span, an exception was made for those applications discussed during the last analysed session of the EAC held on July 1, 2014 (BfArM 2014b). In the absence of evidence of a decision by the BMG and the Bundesrat, these applications were rated *BMG decision not yet available*. *Successful* applications were defined as those with a positive EAC recommendation implemented by the BMG and the Bundesrat. *Unsuccessful* applications were defined as those either recommended for rejection by the EAC (i.e. negative recommendations) or those with a positive EAC recommendation not subsequently followed by the BMG and the Bundesrat.

Results

Number and direction of applications to change prescription status

Between 2009 and 2014, the EAC dealt with 101 applications. Of these, nine regarding veterinary medicines and one concerning a homeopathic preparation were not considered further. The remaining 91 applications were classified into five categories (see Figure 1).



Abbreviations: OTC: Over-the-counter status; Rx: Prescription-only status; BMG: German Ministry of Health; EAC: Expert Advisory Committee for Prescription-Only Issues

Figure 1: Flowchart of EAC recommendations and subsequent BMG/Bundesrat decisions

Applications the EAC recommended rejecting

Rx-to-OTC switch

Regarding Rx-to-OTC switch applications, the EAC recommended accepting the application in 15 (58%) cases and rejecting the application in eight (31%) cases. No decision was made for three (11%) applications. An overview of rejected applications can be found in Table 2.

Table 2: Applications for Rx-to-OTC switches with negative recommendations by the EAC including EAC deliberations

Substance – Usage	Underlying EAC considerations	Comments
Famciclovir – for oral treatment of recurrent episodes of herpes labialis in immunocompetent adults	<p>Applied for indication does not represent a medical emergency</p> <p>Pharmacists may not be able to exclude contraindicated use in patients with renal insufficiency</p> <p>Data on usage experience in ambulatory settings too limited</p>	
Benzydamine – for use in the mouth and throat for the treatment of pain and irritation	Application too broadly formulated	During the same session, the EAC recommended accepting an alternative application that additionally specified the maximum amount of active substance per dosage unit, a maximum concentration of 1.5 mg/ml, and lozenges and solutions as permissible pharmaceutical forms.
Ipratropium bromide – for intranasal use for the treatment of rhinitis	<p>No usage experience with single-agent ipratropium bromide products in Germany</p> <p>Intranasal application may result in higher systemic availability than inhaled use; however, combination products for inhaled use are still Rx</p>	The EAC had already provided a positive recommendation three years earlier (BfArM 2009b) but no transposition into German law had followed. Originally, the applicant had intended to request OTC status for ipratropium bromide in order to obtain OTC status for a drug containing xylometazoline and ipratropium bromide (Unkauf 2009). In 2012, this was formulated in two explicit applications.
Combination of xylometazoline and ipratropium bromide – for the treatment of	Single-agent OTC-available xylometazoline is effective for treating the majority of rhinitis	

rhinitis	<p>cases</p> <p>Compared to OTC-available single-agent xylometazoline, the combination results in more adverse effects, including systemic anticholinergic reactions, which may not be acceptable for treating a self-limiting condition</p> <p>Severe cases of rhinitis should be treated by a physician</p>	
Racecadotril – for oral treatment of acute diarrhoea in adults	Insufficient data on adverse effects and the safety profile in an OTC context	The EAC suggested the licence holder re-apply during a future session (BfArM 2012a). The licence holder did so, resulting in a subsequent positive recommendation on condition that changes in the package leaflet were made (BfArM 2012b).
Rizatriptan – for acute treatment of migraine in adults	Low quality of application and inconsistencies of arguments presented in the submitted materials: insufficient risk-benefit assessment; and application for OTC status for the higher 10mg dose, whereas Rx status for 5mg remained	The topic had already been discussed during an earlier session but the decision had been postponed (BfArM 2011a).
Sumatriptan nasal spray – for the acute treatment of migraine in adults	<p>Strong variability in the onset of action makes the drug unsuitable for the self-medication of acute migraine attacks</p> <p>Unknown risk of misuse within families by children and youths</p>	The application was made again one year later and received a positive recommendation by the EAC, but no transposition into German law followed.
Multibacterial inactivated vaccines – for oral use – e.g. for bacterial pyelonephritis or chronic recurrent respiratory infections	<p>Effectiveness not proven</p> <p>Indication not suitable for self-medication</p> <p>Application was made because statutory health insurance funds were no longer willing to reimburse these drugs, but the EAC has no mandate to solve reimbursement issues</p>	

Increase in OTC availability

Of twelve applications requesting an increase in OTC availability, the EAC recommended rejecting five (BfArM 2010a, 2011a, 2012a, 2014b) (Table 3).

Table 3: Applications for an increase of OTC availability with negative recommendations by the EAC and EAC deliberations

Substance – Usage	Underlying EAC considerations
Racecadotril granules to make a suspension – for the treatment of diarrhoea: Extend OTC availability to children ≥5 years	Limited effectiveness Lack of opportunity to communicate the importance of rehydration in an OTC setting Body weight limits preferable over age limits; but in an OTC setting it may be more difficult to observe body weight limits compared to age limits
Racecadotril granules to make a suspension – for the treatment of diarrhoea: Extend OTC availability to children ≥12 years	OTC use could mask serious diseases
Fluoride toothpaste – for the prevention and treatment of dental caries for patients ≥16 years with a high caries risk: Extend OTC availability to 5 mg/g	Risk of fluoride intoxications that might result from OTC availability cannot be adequately estimated The extent to which childproof closures could mitigate the risk of fluoride intoxication in children is unclear
Vitamin D (D3, cholecalciferol): Increase OTC-available daily dose from 1000 IU to 2000 IU	The application lacks reference to one or more indications No data about long-term effects (e.g. mortality) in submitted materials The potential public health issue of vitamin D deficiency in Germany cannot be resolved by increasing OTC availability of vitamin D
Loperamide – for the treatment of diarrhoea: Extend OTC availability to liquid forms of administration	Liquid forms of administration have no added value in comparison to oral solid forms from a medical point of view Rehydration is preferred over antimotility agents for the treatment of acute diarrhoea. Tablets are therefore preferable over liquid forms of administration as they are administered with higher amounts of liquids

Decrease in OTC availability

The EAC recommended rejecting an application requiring mandatory prescription of pancreatin for the treatment of disorders of the exocrine pancreas that accompany maldigestion. The application sought to limit OTC availability to doses up to 20,000 PhEur units per separate form. The negative EAC recommendation considered two major aspects: Firstly, one intention of the application was

facilitation of reimbursement of pancreatin by the statutory health insurance funds. However, the EAC felt that it was not its responsibility to solve reimbursement issues. Secondly, the EAC argued that it is unlikely that the need to seek medical attention in order to obtain prescriptions could increase the detection of pancreas insufficiency complications or improve the early detection of pancreas carcinoma, as had been put forward by the applicant (BfArM 2010b; Deutsche Gesellschaft für Gastroenterologie 2010).

In 2011, the EAC recommended rejecting an application to restrict the pack size of some OTC nonsteroidal anti-inflammatory drugs (NSAIDs) to a maximum therapy duration of four days. This application concerned acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenazone and propyphenazone (BfArM 2011c). The EAC had previously recommended restricting pack sizes of these NSAIDs to the four-fold maximum daily dose, resulting in pack sizes with a maximum therapy duration between 3.5 and 6.6 days, depending on the active ingredient (BfArM 2010a). However, the former recommendation had not been transposed into German law. The experts referred back to the previous recommendation and it was also discussed that there is little empirical evidence that coupling the recommended duration of use of these OTC NSAIDs with pack size restrictions will make them safer. For acetylsalicylic acid, diclofenac, ibuprofen and naproxen, the EAC revised its recommendation one year later and recommended a pack size restriction adapted to a maximum therapy duration of four days (BfArM 2012b).

The EAC also recommended rejecting an application for mandatory prescription of polihexanide 0.02% and 0.04% for adjuvant antiseptic wound treatment, e.g. after surgical debridement. However, the decision was not preceded by a discussion and the protocol of the relevant session therefore did not mention any reasons for this decision (BfArM 2009a).

OTC-to-Rx switch

Applications to require mandatory prescription for both paracetamol and pseudoephedrine without exceptions were recommended for rejection by the EAC. The discussion preceding the experts' vote on paracetamol was limited to questions about the presentations held by the applicant – an EAC member – and the BfArM (BfArM 2012b). The applicant presented a comparison of the criteria an OTC drug should fulfil and how these, in his perception, were not met by paracetamol. In terms of effectiveness, he argued that paracetamol is unreliable in alleviating osteoarthritis pain, that there is no proven effectiveness for alleviation of lower back pain and that paracetamol is less effective for postoperative pain than other analgesics. In terms of hepatotoxicity, he expanded upon the fact that overdoses can have lethal outcomes. He also presented studies suggesting an increased risk of high blood pressure and stroke resulting from prolonged paracetamol use. He further presented study results suggesting an association between paracetamol intake during pregnancy and an increased

risk of childhood asthma. Lastly, he mentioned the interaction potential of concomitant use of paracetamol and alcohol (Anonymous member of the EAC 2012). The BfArM did not follow the expert's arguments. It argued that paracetamol is the most frequently sold OTC analgesic in Germany and that there is sufficient evidence for its effectiveness: the benefits of NSAIDs over paracetamol in the treatment of osteoarthritis pain are relatively modest; paracetamol is an effective treatment for migraine headaches; NSAIDs are not more effective than paracetamol in the treatment of lower back pain, and paracetamol is effective in the treatment of postoperative pain for about 50% of patients. Further, the presenter on behalf of the BfArM quoted studies showing that increased blood pressure or risk of cardiovascular events have only been found in studies with paracetamol intake on six to seven days per week, or for more than 22 days per month. He also presented findings showing that no causal relationship between prenatal exposure to paracetamol and childhood asthma had been established. No clinically significant liver damage had been observed in studies at therapeutic dosages of paracetamol. Regarding paracetamol overdose, 1.2 hospital admissions per 100,000 people with statutory health insurance were due to paracetamol intoxication in 2010 and 9-17% of all cases of acute liver failure in Germany were considered to be attributable to paracetamol. Finally, the BfArM presentation expanded upon distinct advantages of paracetamol, such as paracetamol being the only OTC analgesic and antipyretic licensed for use during all stages of pregnancy and in infants (BfArM 2012c).

During the deliberations on the application to switch pseudoephedrine from OTC to Rx status, the role of OTC products containing pseudoephedrine in illegal drug production was discussed. It was argued that it would not be financially rewarding to use finished medicinal products with low pseudoephedrine content for this purpose. Recognising this potential problem, however, an alternative application was recommended for acceptance by the experts. Herein, mandatory prescription was required for medicines with pseudoephedrine concentrations of 720 mg per pack or higher (BfArM 2010b).

Discrepancies between EAC recommendations and BMG decisions

If the EAC recommended rejecting an application, the BMG and the Bundesrat followed the recommendation in all cases for which this information is available. In those cases with positive EAC recommendation, however, some discrepancies between the recommendations and transposition into German law were observed (see Table 4).

Table 4: Discrepancies between experts' recommendations and BMG decisions

Category	Number of positive recommendations	BMG and Bundesrat decisions not following the EAC recommendation		Substances concerned
		N	%	
Rx-to-OTC switch	15	4	27	Desloratadine Intranasal ipratropium bromide Oral zolmitriptan Sumatriptan nasal spray
Increase in OTC availability	7	0	0	n/a
Decrease in OTC availability	13	9	69	Acetylsalicylic acid (2 applications) Diclofenac (2 applications) Ibuprofen (2 applications) Naproxen Phenazone Propyphenazone
OTC-to-Rx switch	11	0	0	n/a
Legally neutral changes in wording	7	0	0	n/a

Discrepancies between EAC recommendations and BMG decisions occurred in two categories, *Rx-to-OTC switches* and *decrease in OTC availability*. BMG officers occasionally provided explanations during EAC sessions for why certain recommendations had not been followed. For desloratadine, however, no explanation was provided. For intranasal ipratropium bromide, it was stated that insufficient overall usage experience was the reason for not following the recommendation (BfArM 2012a). The BfArM added that the EAC recommendation had not been followed because the combination of xylometazoline and ipratropium bromide had not been on the market for three years at the time of the decision (BfArM 2012d). Regarding oral zolmitriptan and sumatriptan nasal spray, BMG officers explained that the EAC had recommended an Rx-to-OTC switch only on condition that changes were made to the package leaflet. However, German authorities are not in a position to

change the text of the package leaflet when the drug has been licensed through the European decentralised procedure or the mutual recognition procedure (BfArM 2013).

The BMG explained that the recommendation to restrict the pack sizes of acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenazone and propyphenazone by adapting them to the four-fold maximum daily dose had not been followed because the EAC had based its justifications on pack sizes already available on the market, e.g. had recommended restricting the amount of active ingredient to the smallest available pack size, instead of providing a substance-based recommendation. The BMG explained that this type of justification was insufficient from a legal point of view because justifications for changes to the prescription status need to be based on the properties of the substance as such (BfArM 2011c). A later EAC recommendation to restrict the pack sizes of acetylsalicylic acid, diclofenac, ibuprofen and naproxen to a maximum therapy duration of four days was not transposed into German law either, and the BMG did not provide an explanation to the EAC on this topic.

Discussion

This study showed that of 101 applications to change prescription status, the EAC dealt with 91 applications regarding non-homeopathic medicines for human use between 2009 and 2014. Of these applications, 39 were successful and 30 unsuccessful. For 22 applications, no decision was made or available at the time of writing this article. Applications can be unsuccessful at two levels. Firstly, the EAC can recommend rejecting an application. Secondly, the BMG and the Bundesrat can decide not to follow a recommendation.

Negative recommendations by the EAC

Decrease in OTC availability

The fact that applications for a decrease of OTC availability were also among the unsuccessful ones was an unexpected finding. While unsuccessful applications for Rx-to-OTC switches or successful ones for OTC-to-Rx switches had been reported previously (Cohen 2003; Helmstaedter 1985; Soller et al. 2011; Wessels 2006), regulatory decisions hindering the decrease of OTC availability could not be found in the literature so far. For example, the EAC recommended rejecting the OTC-to-Rx application regarding pseudoephedrine because it considered the risk of finished medicinal products containing pseudoephedrine being misused in the production of illegal drugs low. The subsequent positive recommendation for limiting the OTC-available pseudoephedrine content to 720mg per pack can be interpreted as an attempt to hinder criminal activity with OTC drugs while maintaining the public health benefits of OTC-available pseudoephedrine.

Similar arguments may be true regarding the unsuccessful application for mandatory prescription of paracetamol. While existing data were sometimes interpreted differently by the applicant and the BfArM, it was striking that important arguments put forward by the BfArM considered the benefits associated with the OTC status of paracetamol. However, it should also be noted that the pack size of OTC-available paracetamol had been restricted to 10g prior to our study period in order to decrease the risk of suicides committed with paracetamol (BfArM 2008).

The negative EAC recommendations regarding NSAIDs' pack size restrictions for a maximum duration of four-day-use, in turn, leave room for interpretation. On the one hand, the positive recommendations for pack size restrictions preceding and following these negative recommendations demonstrate a general willingness to restrict the pack sizes of NSAIDs. On the other hand, there is certain discordance among the experts who are challenged with finding evidence-based arguments for linking maximum duration of use with pack size restrictions. The cases of pseudoephedrine, paracetamol and NSAIDs illustrate that EAC decisions recommending not to decrease OTC availability are complex and often take place in the broader context of other decisions on changes to a particular drug's prescription status.

Increase in OTC availability

A lack of OTC suitability or safety concerns presented the most common reasons for negative recommendations for applications regarding an increase in OTC availability. For example, the inability of pharmacists to exclude an OTC drug's contraindications or the OTC drug-associated risk of delaying the diagnosis of serious disease were among the arguments raised. Also, sumatriptan nasal spray was considered unsuitable for self-medication due to a risk of too early repeated use resulting from its highly varying onset of action. Similarly, the EAC expressed concerns that liquid forms of loperamide are not an appropriate pharmaceutical form for the OTC context. In the case of the combination of xylometazoline and ipratropium bromide, it was argued that the indication 'rhinitis' can already be treated effectively with OTC drugs that are comparatively safer. Most of these criteria can also be found in an EU policy-guidance document on the topic, the *Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use*, commonly referred to as the "switch guide" (European Commission 2006) and within the guidance to EAC members provided by the BfArM (Brixius 2013).

Insufficient safety data or a lack of quality of the submitted materials were the second most common reasons for negative recommendations in the case of applications for increased OTC availability. For example, insufficient safety data played a role in the negative recommendations regarding racecadotril. For famciclovir, the data on usage experience in ambulatory settings were too limited. Regarding rizatriptan, the EAC found inconsistent arguments in the submitted materials, in particular

because the external expert applied varying standards in his risk-benefit evaluations. Similarly, the application to increase the OTC availability of cholecalciferol received a negative recommendation because the submitted materials did not include references to one or more indications. Obviously, the EAC has to recommend rejecting applications if the available data or the data in the submitted materials are insufficient, incorrect or inconsistent.

A related category of arguments is limited evidence from drug utilisation research or regarding behavioural aspects of self-medication. For example, the likelihood of in-family misuse in the case of sumatriptan nasal spray or the risk of fluoride intoxications that may result from increased OTC availability of fluoride toothpaste could not be adequately estimated. In the context of the latter, it was also unclear to what extent childproof closures could mitigate the risk of fluoride intoxications in children.

Negative recommendations concerning an increase in OTC availability are in line with the expectation that regulatory bodies may find products unsuitable for use in an OTC context, or cannot conscientiously make a positive recommendation in light of insufficient data. However, as with applications for a decrease in OTC availability, not all decisions should be seen as an absolute judgement of a substance's suitability for the OTC context. On several occasions, the EAC came to different conclusions such as when two comparable applications were made at different points in time, e.g. in the case of ipratropium bromide and sumatriptan nasal spray, or when an unsuccessful application was amended into a more precise application.

BMG/Bundesrat decisions

Most commonly, the BMG and the Bundesrat did not follow EAC recommendations for legal reasons such as the lack of jurisdiction to make additional EAC-requested changes to package leaflets of products licensed by one of the European authorisation procedures. The first recommendation by the EAC to restrict the pack sizes of OTC NSAIDs was not followed by the BMG and the Bundesrat mostly due to legal reasons, including a lack of legal feasibility of non-substance-based justifications.

On one occasion, the BMG decided not to follow an EAC recommendation due to a potential drug safety concern, i.e. the overall insufficient usage experience with intranasal ipratropium bromide. According to German law, switch applications for new substances are permissible at the earliest three years after initial admission to the market (BMJ 1976). The underlying thinking is that pharmacovigilance data i.e., data incorporating 'usage experience', are necessary to make an assessment on drug safety in an OTC context (European Commission 2006). However, it is obvious that the mere availability of a drug on the market will not necessarily result in a high number of users. The discrepant decisions regarding intranasal ipratropium bromide show that the EAC and the

BMG came to different conclusions on whether the usage experience was sufficient for an Rx-to-OTC switch. The later negative EAC recommendation also used similar arguments, for example that there was no usage experience with single-agent ipratropium bromide products. One possible reason for such disparate decisions between stakeholders is the fact that the available safety data are often insufficient as they are only based upon sales data due to a lack of systematic post-marketing safety studies.

Strengths and limitations

This study was entirely based on material available to the general public. This means that the analysis was conducted in a traceable and reproducible way. However, there is some inconsistency between and within session minutes, posing a challenge in disentangling applications from one another. For example, some applications were discussed under the same agenda item, while in other minutes separate agenda items were made for each application. Also, applications that were amended during the course of discussion were sometimes not explicitly mentioned as such. Therefore, it was necessary to compare the session minutes with the results reports in order to check whether the applications that were voted on differed from the applications that had been discussed. While the BfArM is obliged to provide justifications when changes in the prescription status are recommended, this is not the case for negative recommendations. Therefore, reasons for negative recommendations were often not explicitly mentioned in EAC session minutes or their supporting documents. For this reason, arguments exchanged by the experts prior to their negative recommendations were analysed for this paper instead in most cases. As it is unknown to what extent these arguments were relevant to the experts' decisions, the approach we took presents a weakness of this study. Nonetheless, it is the first study from Germany discussing unsuccessful switch applications. Moreover, it adds to the scarce evidence on the topic of regulatory aspects of changes in prescription status other than Rx-to-OTC switches and complements earlier efforts to summarise switches and re-switches in Germany by Helmstaedter (1985) and Wessels (2006).

Conclusions

Negative decisions on applications to change the trade status of drugs in Germany are not infrequent and between 2009 and 2014 most of them related to a decrease in OTC availability. When considering that negative decisions regarded both applications for increases as well as decreases in OTC availability, it becomes clear that regulatory decision-making on changing the trade status of drugs is a complex task. While the question of whether a drug can be used safely in the OTC context is the most important criterion, public health benefits of that drug's OTC availability also play an important role in regulatory practice. Moreover, it is commonly found that unsuccessful applications for changes in drug trade status are not isolated occurrences. Rather, unsuccessful applications are

often preceded or followed by modified successful applications regarding the same substance. This shows that most substances whose trade status has been subject to German regulatory decisions in recent years do not fall unambiguously into either the OTC or the Rx category. Instead, their trade status and possible exceptions thereto are diligently balanced by the regulatory bodies. However, it is not always clear how different considerations are weighed against each other and insufficient data relevant to self-medication remain a common challenge for regulators. It would therefore be desirable if the reasons for both negative and positive recommendations in Germany were communicated more explicitly in order to foster the transparency of regulatory decisions. Also, further research is necessary in the fields of regulatory science and drug utilisation to improve regulatory decision making. Firstly, analysing, identifying and discussing criteria for OTC status from a normative and practical perspective would further improve the understanding of regulatory decision making in this area. Secondly, better insights regarding the actual correct and incorrect use of OTC drugs in the population are desirable to strengthen the evidence base for the risk assessment underlying regulatory decisions on changes to the prescription status of drugs.

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Annex III

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Barrenberg E, Garbe E

**From prescription-only (Rx) to over-the-counter (OTC) status in Germany 2006-2015:
Pharmacological perspectives on regulatory decisions**

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Abstract

Key words: over-the-counter medicines, Rx-to-OTC switch, non-prescription drugs, Germany

Purpose: Little is known about the extent of switches from prescription-only (Rx) to over-the-counter (OTC) status in Europe and about the pharmacological properties of the switched substances. The objective of this study was to provide an overview of the substances that were switched from Rx to OTC status in Germany between 2006 and 2015 and to assess their pharmacological properties.

Methods: Session minutes of the German Expert Advisory Committee for Prescription-Only Issues, changes to the German Ordinance on Prescription-Only Medicines, and the Summary of Product Characteristics of the switched substances were analysed. Pharmacological properties were studied in relation to the EU *Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use* (the 'EU switch guide').

Results: Between 2006 and 2015, seven substances (almotriptan, omeprazole, benzydamine, ibuprofen/pseudoephedrine, racecadotril, ketotifen, levonorgestrel) were switched from Rx to OTC status in Germany. In all cases, the OTC status was restricted to certain indications, doses, pack sizes, or other limitations. Notwithstanding recommendations of the EU switch guide, some of the switched substances might interact with commonly used drugs potentially resulting in serious adverse drug reactions, or have contraindications or warnings regarding substantial parts of the population.

Conclusions: The stipulations of the EU switch guide were fully met for only some switches, while this was not completely the case for others. Further development of guidance on balancing risks and benefits of OTC availability is recommended.

Introduction

About half of all packs sold in German pharmacies are over-the-counter (OTC) drugs [1]. Self-medication with such drugs thus forms a substantial part of the pharmaceutical supply of the German population. At the same time, OTC drugs receive rather limited attention in the drug regulatory and pharmacological literature.

Researchers have discussed the increased availability of OTC drugs and their public health implications [2-5], and they have evaluated previous switches in public health [6], economic [7], and sociological terms [8]. They have also addressed criteria OTC drugs should fulfil [9-11], discussed whether certain substances should be available OTC or not [12-14], commented on decisions of switch advisory committees in the United States of America [15], and studied views on regulatory considerations in different countries [16, 17]. Most recently, Kroth discussed German switch

developments in comparison to other countries [18]. However, not much normative literature is available regarding regulation of Rx-to-OTC drug switches, and there are no explicit criteria for when to switch.

In the European Union (EU), a policy-guidance document, the *Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use* (the 'EU switch guide') was published in 1998 and revised in 2006 [19, 20]. The switch guide provides guidance on pharmacological properties of drugs which are considered for a switch including the following principles: OTC drugs should in general have low toxicity, they should have a low risk of serious type A reactions and a very low risk of serious type B reactions, and they should have "no interactions with commonly used medicines which can produce serious adverse reactions" [20]. In view of the risk of masking serious diseases by the use of OTC drugs and delaying diagnoses, OTC status should be approved "primarily for short-term treatment". Contraindications, interactions, warnings and precautions should not have a high incidence or "a high rate of usage of interacting drugs in the population". The health risk of OTC drugs must be small in case of off-label usage and drugs should not become OTC if there is known incorrect (e.g., recreational) use [20].

The present study complements earlier work by the authors on unsuccessful switch applications in Germany between 2009 and 2014 [21]. It aimed to contribute further insights into switches in drug prescription status in Germany by addressing the following two research questions: (1) Which substances have been switched from prescription-only to over-the-counter status (i.e., pharmacy-only OTC drugs) in Germany between 2006 and spring 2015? (2) What are the pharmacological properties and therapeutic indications of these substances in relation to the considerations laid out in the EU switch guide?

Methods

Scope and Data sources

In Germany, there are two classes of OTC drugs: pharmacy-only and general sales drugs. The scope of the present study was limited to switches from Rx status to pharmacy-only OTC status. Applications for such switches are addressed to the German Federal Institute for Drugs and Medical Devices [BfArM] [22]. BfArM provides the secretariat for the external Expert Advisory Committee for Prescription-Only Issues (EAC) which makes recommendations about a drug's prescription status to the Ministry of Health [23]. The ministry in turn takes the final decision in agreement with the Federal Council of Germany (*Bundesrat – the constitutional body where the sixteen German Bundesländer (federal states) jointly legislate* [24]) [25]. Substances with Rx status and exceptions thereto are listed and updated regularly in the Annex of the Ordinance on Prescription-Only

Medicines [26]. For the study, all minutes of the German EAC sessions available online in September 2015 dating back to January 2006 including their supporting documents were reviewed (www.bfarm.de/DE/Arzneimittel/Pharmakovigilanz/Gremien/Verschreibungspflicht/_node.html). To ascertain for which substances recommendations for Rx-to-OTC switches were implemented, all subsequent changes to the Ordinance on Prescription-Only Medicines were searched until March 2015. A comprehensive list of all data sources is provided in the supplementary materials. The present study was limited to national switch applications that are handled as per the described procedures and did not address switches that have occurred through the European centralized switch procedure. The EAC can be consulted as regards the transposition of centralized switches into German law, but cannot advise on the switch applications as such [27, 28].

In order to study the pharmacological properties and therapeutic indications of the substances in question in relation to the EU switch guide, the Summaries of Product Characteristics (SPCs) were used as primary source of information. Data on the prescribed and dispensed defined daily doses (DDDs) of these drugs in 2014 were obtained from the annual German Drug Prescription Report 2015 [29]. All reviewed sources are listed in the supplementary materials A.

Assessment of switched substances, their pharmacological properties, and therapeutic indications

Only substances for which a legal change was implemented after the switch recommendation by the EAC were considered. Because Rx-to-OTC switches are often limited to certain doses, indications, user groups or similar characteristics, exceptions from Rx status were presented in the way they were specified in the Ordinance on Prescription-Only Medicines. Special cases, e.g., where the OTC status was intended only for specific professions (e.g., naturopaths or midwives), or where the switch decision aligned the legal with a de-facto situation, were excluded from our analysis.

Based on the recommendations of the EU switch guide, the switched substances were analysed according to the following aspects: Indications, contraindications, precautions and warnings, interactions, and serious adverse drug reactions (ADRs).

Indications were studied according to whether the substances are intended to treat acute or chronic conditions. Contraindications were classified as follows: Hypersensitivity reactions to (1) the active ingredient or excipients and (2) the substance class; contraindications based on (3) illness in patient history, (4) currently present illness and (5) risk factors; (6) contraindications related to special population groups; (7) concomitant drug use; and (8) contraindications related to indication of use. Similarly, precautions and warnings were analysed according to the following categories: Warnings that refer to (1) food intolerances in relation to drugs' excipients, (2) illness in patient history, (3) risk factors, (4) special population groups, (5) concomitant drug use, (6) indication of use, (7) ADRs, and

(8) instructions for use. Interactions with commonly used drugs that can cause serious ADRs were studied considering the prescribed and dispensed DDDs of the interacting substances in Germany in 2014 for the classification of common use [29]. For the purpose of this study, substances or substance classes were defined as “commonly used” if they ranked among the 70 most prescribed and dispensed substances in outpatient settings, corresponding approximately to more than 100 million DDDs in 2014 [30]. Frequencies of serious ADRs were assessed according to the EU guideline on SPCs [31]. A distinction between type A and type B ADRs was not made.

Our working definition of ‘serious’ ADRs was based on WHO guidelines defining a serious ADR as ‘results in death’, ‘is life-threatening’, ‘requires inpatient hospitalisation or results in prolongation of existing hospitalisation’, ‘results in persistent or significant disability/incapacity’, ‘is a congenital anomaly/birth defect’, ‘is a medically important event or reaction’ [32]. Diseases which may take less severe courses but might also require hospitalization or result in death in certain instances were assessed as ‘serious ADRs’ for the purpose of this study.

Results

Switched substances

Between 2006 and 2014, ten single substances and one combination drug received a positive switch recommendation from Rx to OTC status enacted into law by spring 2015. Of these, four substances represented special cases. Three of these special cases (lidocaine, epinephrine and dexamethasone) were made available OTC only for midwives and naturopaths. Myrtecaine presented the fourth special case: it was already being sold OTC, but due to a coding error when revising German drug law, myrtecaine had become an Rx substance from a legal point of view; the Rx-to-OTC switch was thus made to align the legal situation with reality. These special cases were not considered further in this study as the provisions on the EU switch guide relate to OTC availability for the general public. Table 1 presents an overview of the switched substances, the years of recommendation and implementation, and the wording of the exception added to the prescription status.

Table 1: Rx-to-OTC switches in Germany from 2006–2015 with the respective exceptions to Rx status

Year of recommendation	Year of implementation	Substance or combination	Wording of exception to prescription status
2007	2009	Almotriptan	For the acute treatment of the headache phase of migraines with and without aura in adults between 18 and 65 years, after an initial diagnosis by a physician, in solid preparations for oral use at concentrations of 12.5 mg per separate form and a total amount of 25 mg per pack

2009	2009	Omeprazole	For treatment of heartburn and acid regurgitation <ul style="list-style-type: none"> - in a single dose of 20 mg, - in a maximum daily dose of 20 mg, - with a therapy duration limited to a maximum of 14 days, and - in a maximum pack size with 280 mg of the active substance
2012	2013	Benzydamine	- As a solution for use in the mouth and throat with a concentration of no more than 0.15% (1.5 mg/ml) <ul style="list-style-type: none"> - As a lozenge for use in the mouth and throat with a maximum amount of 3 mg benzydamine hydrochloride per separate form
2012	2013	Ibuprofen / Pseudo-ephedrine	Ibuprofen for oral use (in a maximum single dose of 400 mg and a maximum daily dose of 1200 mg) in combination with pseudoephedrinehydrochloride (in a maximum single dose of 60 mg and a maximum daily dose of 180 mg) with a maximum amount of active substance of up to 4800 mg ibuprofen and 720 mg pseudoephedrine per pack, for the treatment of acute rhinosinusitis in the context of further symptoms of colds (e.g., fever and pain)
2012	2013	Racecadotril	For the symptomatic treatment of acute diarrhoea in adults (≥ 18 years of age), as solid preparation for oral use as a hard capsule, in concentrations of 100 mg per separate form and with a duration of use for up to 3 days and pack sizes of up to 10 hard capsules provided that the SPC and the package leaflet specify: <ul style="list-style-type: none"> a) the contraindication that racecadotril must not be used for diarrhoea that is accompanied by fever, bloody or mucosal stools as these symptoms can indicate the presence of invasive bacteria or other severe diseases, or for diarrhoea that occurs after antibiotic-intake (pseudomembranous colitis), and b) the warning that racecadotril should only be used after medical consultation in case of an acute phase of ulcerative colitis or in case of kidney or liver insufficiency
2014	2014	Ketotifen	For use in the eye in a concentration of up to 0.025 %
2014	2015	Levonorgestrel	In preparations for emergency contraception without the addition of medically active ingredients for the one-time oral use in a single dose of up to 1.5 mg and a total amount of 1.5 mg per pack

Pharmacological properties and therapeutic indications of the switched substances

Indications

Levonorgestrel for emergency contraception is intended for one-off use and three of the substances are intended for the treatment of predominantly acute conditions: Benzydamine for the symptomatic treatment of pain and irritations in mouth and throat; ibuprofen/pseudoephedrine for

the symptomatic treatment of rhinosinusitis co-occurring with headache, fever, and cold-related pain; and racecadotril for the symptomatic treatment of acute diarrhoea.

In contrast, almotriptan indicated for the acute treatment of the headache phase of migraine attacks with and without aura, and ketotifen indicated for the symptomatic treatment of seasonal allergic conjunctivitis are both intended for the treatment of acute, but often recurring conditions. Heartburn or symptoms of reflux disease as indication for omeprazole use can also take a chronic course.

Contraindications

For benzydamine, ketotifen, and levonorgestrel the only contraindications listed in the SPCs are hypersensitivity reactions to the active ingredient or excipients. The use of almotriptan and ibuprofen/pseudoephedrine are contraindicated for patients with a history of myocardial infarctions and currently present severe or uncontrolled (mild or moderate) hypertension. The use of almotriptan is also contraindicated in patients with a history of or currently present angina pectoris, asymptomatic myocardial ischaemia and Prinzmetal angina, or a history of stroke, a transient ischaemic attack or peripheral vascular disease. A complete list of contraindications can be found in the supplementary materials B.

Precautions and warnings

No precautions or warnings were included in the SPC of ketotifen. For almotriptan, precautions and warnings included uncontrolled hypertension, diabetes mellitus and hypercholesterolaemia and for ibuprofen/pseudoephedrine, they included, among others, hypertension, heart disease/cardiac insufficiency and hyperthyroidism. As regards special population groups, precautions and warnings for almotriptan exist for women after menopause, men aged >40 years, people with obesity, smokers, and elderly patients. For ibuprofen/pseudoephedrine such include paediatric and elderly patients. A full list of precautions and warnings for all studied substances can be found in the supplementary materials B.

Interactions

Twenty-three interacting substances/substance classes were found for which serious adverse reactions were reported in the SPCs. On 14 occasions, the interacting substances/substance classes were commonly used as per our definition and exceeded 100 million DDDs. These interactions regarded almotriptan and ibuprofen/pseudoephedrine (table 2).

Table 2: Interactions that can cause serious ADRs and amount of DDDs prescribed and dispensed in Germany in 2014

Interacting substance or substance class	DDD in million	Possible serious adverse reactions
Almotriptan		
SNRIs	235.8	Serotonin syndrome-like symptoms
SSRIs	596.7	
Ibuprofen/pseudoephedrine		
Indirectly acting orally or nasally applied sympathomimetic drugs, vasoconstrictive drugs, or α -sympathomimetic drugs	144.4 ^a	Risk of vasoconstriction and/or hypertensive crisis
Digitalis glycosides	112.2	Increased occurrence of arrhythmia
Tricyclic antidepressants	266.3	
Other NSAIDs	1711.8 ^b	Increased risk of gastrointestinal ulcerations and bleedings
Corticosteroids	424.5	Increased risk of gastrointestinal bleedings
Thrombocyte aggregation inhibitors	881.6	
SSRIs	596.7	
Angiotensin-converting-enzyme (ACE) inhibitors	5750.0 ^c	In patients with compromised kidney function: Risk of further deterioration of kidney function, including possible acute kidney injury, which is usually reversible
Beta receptor blockers	2282.0	
Angiotensin II receptor antagonists	2592.2 ^c	Risk of hyperkalemia
Potassium-sparing diuretics	232.2 ^d	
Heparines	141.37	Increased risk of bleedings
^a includes: Xylometazoline and its combinations for nasal applications; oxymetazoline for nasal applications ^b includes: Acetylsalicylic acid (ASA)100mg and its combinations; ASA; diclofenac and its combinations; ibuprofen; indomethacin; piroxicam; naproxen and its combinations; meloxicam; dexketoprofen; ketoprofen; dexibuprofen; aceclofenac; phenylbutazone; etoricoxib; celecoxib ^c including combinations with diuretics and calcium antagonists ^d includes: Eplerenone; spironolactone and its combinations; triamterene combinations; amiloride combinations		

Serious adverse drug reactions

Serious ADRs are not listed in the SPCs for ketotifen and levonorgestrel. Serious ADRs of the other substances are presented in table 3 in conjunction with their frequency levels.

Table 3: Serious adverse drug reactions

Frequency level	Substance/combination
Uncommon ≥1/1,000 to <1/100	Ibuprofen/pseudoephedrine: <ul style="list-style-type: none"> - Gastric ulcers with bleedings and/or perforation
Rare ≥1/10,000, <1/1,000	Omeprazole: <ul style="list-style-type: none"> - Angioedema and anaphylactic shock - Depression - Hepatitis with and without jaundice - Hyponatraemia
Very rare ≥1/10,000 to <1/1,000	Almotriptan: <ul style="list-style-type: none"> - Myocardial infarction Omeprazole: <ul style="list-style-type: none"> - Agranulocytosis - Liver failure Benzydamine: <ul style="list-style-type: none"> - Angioedema Ibuprofen/pseudoephedrine: <ul style="list-style-type: none"> - Agranulocytosis - Myocardial infarction - Liver failure - Acute hepatitis - Acute kidney injury - Depression - Pancreatitis - Toxic epidermal necrolysis - Nephrotic syndrome
Frequency not known	Almotriptan: <ul style="list-style-type: none"> - Anaphylactic reactions, angioedema Benzydamine: <ul style="list-style-type: none"> - Anaphylactic reactions Ibuprofen/pseudoephedrine: <ul style="list-style-type: none"> - Haemorrhagic stroke - Ischaemic stroke - Seizures - Exacerbation of infectious inflammations (e.g., necrotising fasciitis) in patients with auto-immune diseases Racecadotril: <ul style="list-style-type: none"> - Angioedema

Discussion

Frequency of Rx-to-OTC switches

Six substances and one combination of substances were switched from Rx to OTC status for general population use in Germany over a period of eight years. This is comparable to five or six ‘innovative’ switches observed in the Netherlands, Australia and the USA between 2003 and 2013, but lower than 11-16 ‘innovative’ switches in Japan, the United Kingdom of Great Britain and Northern Ireland, and New Zealand [33]. The number of seven switches in Germany during recent years is comparatively low compared to 36 switches between 1990 and 2000 as well as 18 switches between 1971 and 1983 [34, 35]. This trend has also been observed in several other countries, including the USA, where Soller found a peak of switches in the period 1992-2001 [36]. According to industry-oriented research, all obvious switch candidates were already switched in the last decades, and it is deemed necessary to find new candidate drugs for Rx-to-OTC switches among those traditionally not considered for self-medication, such as those for chronic diseases [18, 19, 37]. The German switch of almotriptan applied for in 2007 and implemented in 2009 was about at the same time of triptan switches in the UK and New Zealand in 2006. Similarly, the German switch of omeprazole in 2009 followed shortly after the switch of proton pump inhibitors in the UK, New Zealand, the Netherlands, the USA and Australia. In contrast, the switch of levonorgestrel in 2015 came about a decade later in Germany than the switch of emergency hormonal contraceptives in the aforementioned countries [33]. However, there had been an attempt to switch levonorgestrel in Germany in 2003 already [38], but it was followed by an intense public and political debate. The switch decision of 2014/15 was eventually evoked by the European centralized switch of ulipristal acetate [39, 40].

Our study showed that in recent years no unrestricted switches have occurred in Germany. Rather, for every successful application, the OTC availability was restricted in terms of one or more of the following: Indication, user group, active substance per dosage unit, pack size, single dose, maximum daily dose, duration, site of application, route of application, pharmaceutical form or other specifications.

Short-term treatment

Most OTC drugs are intended for acute, often self-limiting conditions. We showed that among the seven studied substances, three were intended for the acute treatment of conditions that can also be recurring or can take chronic courses. In five cases, the exception from Rx status was subject to pack size and/or duration of use restrictions. The Rx-to-OTC switch of almotriptan is in line with the EU switch guide stipulation that OTC status should be approved “primarily for short-term treatment” [20]. While migraine is a recurring condition, the switched substance is intended for the treatment of acute headache phases of migraine. The restriction to two tablets per pack can be considered a

means to discourage prolonged use. Similarly, OTC omeprazole is intended to treat symptoms such as heartburn or acid regurgitation. While these may occur only occasionally, they may also be chronic in patients with severe reflux oesophagitis. However, in the OTC context, if symptoms persist, it is important to enable differential diagnosis, as the same or similar symptoms may have a range of underlying pathologies. The regulatory decision for the Rx-to-OTC switch reflects this concern by limiting the OTC availability to certain indications, a 14-day maximum duration of use and a restricted pack size.

The Rx-to-OTC switch of racecadotril and ibuprofen/pseudoephedrine involved a restricted duration of use of three and five days, respectively. In both cases, pack size restrictions for OTC availability approximately correspond to the duration of these use restrictions. Regarding racecadotril, the maximum duration of use was already stated in the original application by the applicant to prevent masking of serious diseases [41]. In the case of levonorgestrel, the indication 'emergency contraception' implies that it is intended for single use only which is supported by a corresponding pack size restriction. During its deliberations, the EAC also discussed the risk of repeated use, but followed the argument that due to the commonly experienced undesired menstrual changes, the misuse of emergency-contraception levonorgestrel for continuous contraception was unlikely [40].

The question of whether the restriction of pack sizes provides an efficient or sufficient safeguard in limiting the duration of OTC drug use has been much debated within the EAC [27, 42-44]. While the EU switch guide states that "a small pack size is a possible safeguard against misuse, particularly overdose, or a delay in seeking medical attention" [20], empirical evidence on the effectiveness of this measure is lacking. Several researchers studied the impact of OTC paracetamol pack size restrictions on the occurrence of intentional overdose and suicide rates, but the effects remained unclear [45-49]. There have been no scientific studies on the effects of pack size restrictions on patient compliance in the OTC context in Germany.

Frequency of contraindications, interactions, warnings and precautions

According to the EU switch guide, the frequency of contraindications, interactions, warnings and precautions should be low. Our study has highlighted several contraindications, precautions and warnings concerning a substantial percentage of the population. For example, several of the contraindications of ibuprofen/pseudoephedrine and almotriptan refer to conditions affecting significant parts of the population as, e.g., myocardial infarction and coronary heart disease. Their life-time prevalence among German adults aged 40-79 years has been reported with 5% and 9%, respectively [50]. Another contraindication of these two OTC drugs is uncontrolled hypertension, which has been reported in 15% of Germans aged 18-79 years from 2008 to 2011 [51].

Similarly, some of the conditions and risk factors among the precautions and warnings are quite prevalent in the German population. For example, hypertension, a warning listed for ibuprofen/pseudoephedrine has been reported in 32% of the population aged 18-79 years [51]. Other examples concern the precautions and warnings of almotriptan: Highly elevated total serum cholesterol levels of $\geq 240\text{mg}/100\text{ml}$ were present in 20% of women and 18% of men aged between 18 and 79 years [52]. In the same population, obesity was found in 23% of men and in 24% of women [53], and the twelve-month prevalence of physician-diagnosed diabetes mellitus among adults ≥ 18 years was 8% in 2012 [54]. Moreover, in 2012, the Robert Koch-Institut (*German Epidemiological Institute*) estimated that 28% of the German adult population are current smokers [55].

Not for all substances, detailed EAC considerations regarding contraindications, interactions, warnings and precautions are available in the minutes. For example, EAC considerations regarding almotriptan were not detailed in the minutes, since reference was made to the minutes of the earlier naratriptan switch [56]. As regards ibuprofen/pseudoephedrine, an external expert presented results of a pharmacy-based study on real-life uses of an ASA/pseudoephedrine OTC drug, which found high levels of compliance in terms of dosing and duration of use, but did not expand upon contraindications, etc. [57, 58]. An example of more detailed considerations made by the EAC when advising on the switch application for levonorgestrel can be found in the supplementary materials C.

Unlike in the USA, it is not within the German tradition of switch regulation to require self-selection, label-comprehension or actual-use studies [36, 59]. Also, the switch guide does not require evidence that the drug works properly in an OTC-setting, but does not preclude regulators from doing so [20]. Further research is necessary on how the evidence base supporting switch decisions can be strengthened in the European context.

Interactions

For benzydamine, omeprazole, ketotifen, racecadotril, and levonorgestrel “no interactions with commonly used medicines which can produce serious adverse reactions” [20] were found. Regarding almotriptan and ibuprofen/pseudoephedrine, 14 substances/substance classes that are commonly used were identified where in some cases an interaction may produce serious ADRs. For example, it has been indicated that SSRIs, of which 596.7 million DDDs have been dispensed in 2014, can cause serotonin syndrome-like symptoms when interacting with almotriptan and gastrointestinal bleedings when interacting with ibuprofen/pseudoephedrine. The amounts of prescribed heart medication which interact with ibuprofen/pseudoephedrine even exceed the number of prescriptions of SSRIs

and other substances by one order of magnitude. However, the related serious ADR concerns “patients with compromised kidney function” and is described as “risk of further deterioration of kidney function, including possible acute kidney injury, which is usually reversible” [60]. It can be assumed that such patients receive regular medical attention. Therefore interactions with heart medication may be less relevant for the OTC context than the other presented interactions. An analysis of analgesic combinations in a cohort of German patients aged 65-85 years found 235 cases (corresponding to 218 out of 3189 patients) of concomitant analgesic use that can potentially produce serious ADRs. Of these, an OTC analgesic – mostly ibuprofen – was involved in 43 (18.3%) cases [61].

Because the EU switch guide does not provide a definition of the frequency of ‘commonly used’ medications, we chose a definition for the purpose of this study as described in the methods. Our findings of 14 interactions potentially resulting in serious ADRs highlight the need for more clarity of switch guidance at EU and national levels.

Serious adverse drug reactions

There is agreement that the risk of serious ADRs should be low in OTC drugs [11, 20, 62], although there is no rule what frequency level of serious ADRs is considered acceptable for OTC drugs. Ibuprofen/pseudoephedrine is remarkable in this regard. When looking at the highest reported frequency level of serious ADRs, it is the only one of the studied OTC drugs for which serious ADRs were reported at the frequency level ‘uncommon’ corresponding to a frequency of $\geq 1/1.000$ to $< 1/100$. For all other OTC drugs studied, frequency levels were below this level. At the moment when the almotriptan switch was debated, BfArM had only 16 ADRs for almotriptan in its spontaneous reports data base [63]. Schmiedl et al. studied ADR-related hospital admissions and found that out of 6887 patients admitted due to an ADR, only 143 (2.0%) were caused by OTC drugs. Out of these 164 patients, ibuprofen was considered causative in 13.4%, which is only 0.3% out of all ADR-related hospital admissions [64]. Since no benchmarks exist on the permitted frequency of potential serious ADRs, our findings and this discussion illustrate the importance of case-by-case regulatory decisions on Rx-to-OTC switches.

Strengths and limitations

This study contributes to the understudied area of Rx-to-OTC switches in Germany by looking at pharmacological properties and therapeutic indications of recently switched substances. EAC session minutes were only available starting in 2006. Therefore, possible trends in switching over a larger time frame could not be studied. However, in this way, the study was entirely based on materials that are publicly accessible, which allows for reproducibility. Since the considerations in the EU switch guide about pharmacological properties of OTC drugs do not always provide clear definitions,

it was not possible to discuss the findings against an established normative framework for Rx-to-OTC drug switches. For example, the EU switch guide mentions interactions with ‘commonly used’ drugs, but does not provide a definition of ‘common use’. Therefore, we had to define it based on DDDs of the 70 most commonly prescribed and dispensed drugs.

Conclusions

Granting OTC status in Germany during recent years was usually restricted to either certain indications, or low doses, small pack sizes, or other restrictions. The seven switched substances studied in this paper cover a range of pharmacological properties and therapeutic indications. Notwithstanding recommendations of the EU switch guide, some of the switched substances might interact with commonly used drugs potentially resulting in serious ADRs, and some have contraindications, precautions and warnings that concern substantial parts of the population.

It is beyond the scope and purpose of this study to judge whether the Rx-to-OTC switches studied in this paper were appropriate decisions. Instead, we showed that some switches fully correspond to the stipulations laid out in the EU switch guide while this is not completely the case for other switches. As a policy guidance document, the EU switch guide cannot fully cover every aspect of the individual Rx-to-OTC switch decisions. The switch guide mainly focuses on risks arising from OTC availability, while it is conceivable that the EAC balances risks and benefits when advising on Rx-to-OTC switch applications. Further research on how to improve the EU switch guide in light of practical decision-making should therefore be conducted. At the same time, a sound framework for national switch regulation complementing the EU switch guide would be desirable. Against this background, BfArM and the EAC could develop a set of guiding questions and identify research needs to facilitate structured and evidence-based assessments of Rx-to-OTC switch applications.

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Contributions of authors statement: EB and EG jointly developed the research idea and conceptualised the study. EB conducted the data analysis and prepared the manuscript, EG provided substantive intellectual input and critically reviewed the manuscript.

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Supplementary materials A of annex III: Data sources

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Supplementary materials B of annex III: Tables

Table 1: Overview of contraindications

Type of contraindication	Substances concerned
Hypersensitivity reactions to the active ingredient and/or excipients	Almotriptan Omeprazole Benzydamine Ibuprofen/pseudoephedrine Racecadotril Ketotifen Levonorgestrel
Hypersensitivity reactions to the substance class	Omeprazole: - Substituted benzimidazoles Ibuprofen/pseudoephedrine: - Nonsteroidal anti-inflammatory drug (NSAID)-induced asthma
Illness in patient history	Almotriptan: - Myocardial infarction - Angina pectoris - Asymptomatic myocardial ischaemia - Prinzmetal angina - Stroke - Transient ischaemic attack - Peripheral vascular disease Ibuprofen/pseudoephedrine: - NSAID-induced gastrointestinal bleeding or perforation - ≥ 2 episodes of peptic ulcer or gastric haemorrhage - Stroke - Myocardial infarction - Seizures
Currently present illness	Almotriptan: - Myocardial infarction - Angina pectoris - Diagnosed asymptomatic myocardial ischemia - Prinzmetal angina - Severe hypertension (>180/>110 mmHg) - Uncontrolled mild or moderate hypertension (>140/>90 mmHg) - Severe liver insufficiency Ibuprofen/pseudoephedrine: - Peptic ulcer or gastric haemorrhage - Cerebrovascular or other bleedings - Unexplained haematopoiesis dysfunction - Severe liver insufficiency - Severe kidney insufficiency - Severe cardiac insufficiency - Severe or uncontrolled hypertension - Systemic lupus erythematosus
Risk factors	Ibuprofen/pseudoephedrine:

	<ul style="list-style-type: none"> - Increased risk of stroke - Increased risk of narrow-angle glaucoma - Increased risk of urinary retention due to enlarged prostate
Special population groups	<p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Patients <15 years - Pregnant and lactating women - Women of reproductive age not using contraception due to the wish to conceive a child
Concomitant drug use	<p>Almotriptan:</p> <ul style="list-style-type: none"> - 5-HT_{1B/1D}-receptor agonists <p>Omeprazole:</p> <ul style="list-style-type: none"> - Nelfinavir <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Other orally or nasally applied vasoconstrictive drugs - Methylphenidate - Monoamine oxidase inhibitors
Contraindication related to indication of use	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Not to be used for migraine prevention <p>Racecadotril:</p> <p>Not to be used for:</p> <ul style="list-style-type: none"> - Bloody or mucosal diarrhoea - Diarrhoea accompanied by fever - Antibiotic-induced diarrhoea - Chronic diarrhoea: Only after consulting a physician

Table 2: Overview of precautions and warnings

Type of precaution/warning	Substances concerned
Warnings that refer to food intolerances in relation to the excipients of the preparation	<p>Omeprazole</p> <p>Benzydamine</p> <p>Ibuprofen/pseudoephedrine</p> <p>Racecadotril</p> <p>Levonorgestrel</p>
Illness in patient history	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Significant family history of cardiovascular diseases <p>Omeprazole:</p> <ul style="list-style-type: none"> - Peptic ulcer - Gastrointestinal surgery <p>Benzydamine:</p> <ul style="list-style-type: none"> - Asthma <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Seizures - Peptic ulcers - Gastrointestinal toxicity, especially gastric bleedings <p>Levonorgestrel:</p> <ul style="list-style-type: none"> - Thromboembolic events
Currently present condition	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Uncontrolled hypertension - Hypercholesterolaemia - Diabetes mellitus

	<ul style="list-style-type: none"> - Hypersensitivity to sulphonamides - Severe kidney dysfunction - Mild or moderate liver insufficiency <p>Omeprazole:</p> <ul style="list-style-type: none"> - ≥ 4 weeks of symptomatic treatment for digestive disorders or reflux - Jaundice - Severe liver disease <p>Benzydamine:</p> <ul style="list-style-type: none"> - Hypersensitivity to NSAIDs - Asthma <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Hypertension - Heart disease/cardiac insufficiency - Hyperthyroidism - Psychosis - Systemic lupus erythematosus - Connective tissue disease - Prostate enlargement - Chronic sinusitis - Nasal polyps - Ulcerative colitis - Crohn's disease - Chronic liver insufficiency - Chronic kidney insufficiency - Hypovolaemia after major surgical intervention <p>Racecadotril:</p> <ul style="list-style-type: none"> - Acute episode of ulcerative colitis - Kidney insufficiency - Liver insufficiency - Malabsorption due to ongoing vomiting <p>Levonorgestrel:</p> <ul style="list-style-type: none"> - Severe liver insufficiency - Limited efficacy in women with malabsorption syndromes such as Crohn's disease
Risk factors	<p>Levonorgestrel</p> <ul style="list-style-type: none"> - Risk factors for thromboembolic events in patient or her family
Special population groups	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Women after menopause - Men >40 years - People with obesity - Smokers - Elderly patients <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Paediatric patients - Elderly patients - Patients >60 years <p>Levonorgestrel:</p> <ul style="list-style-type: none"> - Women with a high body mass index
Concomitant drug use	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Selective serotonin re-uptake inhibitors (SSRIs)

	<ul style="list-style-type: none"> - Selective norepinephrine re-uptake inhibitors (SNRIs) - Ergotamine-containing drugs - St. John's wort <p>Omeprazole:</p> <ul style="list-style-type: none"> - Atazanavir - Clopidogrel <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Cyclooxygenase-2-inhibitors - Other migraine drugs, especially vasoconstrictive ergot alkaloids - Drugs which lower the threshold for seizures - Volatile halogenated anaesthetics - Lobenguane sulfate I 131 - Oral corticosteroids - Anticoagulants - SSRIs - Antiplatelets - Diuretics <p>Levonorgestrel:</p> <ul style="list-style-type: none"> - Ulipristal acetate
Warnings related to indication of use	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Only to be used after migraine has definitely been diagnosed - Must not be used to treat basilar, hemiplegic or opthalmoplegic migraines - Severe neurological disorders need to be excluded prior to use <p>Omeprazole:</p> <ul style="list-style-type: none"> - In case of troubling symptoms (e.g., sudden decrease in weight, repeated vomiting, melaena) and suspected gastric ulcer, malignancy should be excluded - Should not be used for prevention <p>Benzydamine:</p> <ul style="list-style-type: none"> - If ulcers in mouth and throat persist for >3 days without improvement or are accompanied by fever or other symptoms, medical attention needs to be sought <p>Racecadotril:</p> <ul style="list-style-type: none"> - Parallel rehydration measures need to be maintained <p>Levonorgestrel:</p> <ul style="list-style-type: none"> - If a pregnancy occurs after the use of levonorgestrel, an ectopic pregnancy should be excluded
Warnings related to adverse effects	<p>Almotriptan:</p> <ul style="list-style-type: none"> - Cerebrovascular conditions - If symptoms similar to those of ischaemic heart disease occur - Medication-induced headaches <p>Omeprazole:</p> <ul style="list-style-type: none"> - Salmonellosis and campylobacteriosis <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - Tachycardia - Hypertension - Palpitations - Arrhythmia - Nausea - Neurological symptoms

	<ul style="list-style-type: none"> - NSAID-induced asthma - Skin rashes or mucosal lesions - Visual disturbances <p>Racecadotril:</p> <ul style="list-style-type: none"> - Severe skin reactions
Warnings related to instructions for use	<p>Almotriptan:</p> <ul style="list-style-type: none"> - The recommended maximum dose must not be exceeded <p>Omeprazole:</p> <ul style="list-style-type: none"> - Patients with long-term symptoms such as digestion disorders or reflux should consult a physician <p>Ibuprofen/pseudoephedrine:</p> <ul style="list-style-type: none"> - The dose, the recommended maximum duration of use and the contraindications absolutely need to be respected

Supplementary materials C of annex III: Aspects of EAC considerations – Rx-to-OTC switch of Levonorgestrel as Emergency Contraception

Aspects	Considerations
Primary Mode of Action	<ul style="list-style-type: none"> - Levonorgestrel's (LNG) primary mode of action is blocking ovulation and / or delaying ovulation by suppressing LH peaks.
Approval status, efficacy, and dosing	<ul style="list-style-type: none"> - LNG is approved only to be taken within 72 hours of unprotected intercourse due to subsequent lack of efficacy beyond this time point. - A study that has been designated "controversial" suggests that LNG may be less effective in women with greater body weight, which will be further investigated at the European level. In light of the overall high level of safety of LNG, the so far insufficient evidence for a reduction in efficacy was not considered relevant to the question of an Rx-to-OTC switch (BfArM). - A single dose now replaces the standard two step regimen (0.75 mg taken twice within 12 h) with comparable tolerability, efficacy and good compliance.
Contraindications	<ul style="list-style-type: none"> - The World Health Organization recommends LNG for emergency contraception and emphasises the absence of contraindications.
Toxicity	<ul style="list-style-type: none"> - A variety of prescription drugs currently available are considerably more toxic than levonorgestrel, for example, diclofenac triples the risk of mortality (EAC expert).
Adverse drug reactions	<ul style="list-style-type: none"> - LNG is only associated with mild adverse drug reactions of temporary nature. - There have been no reports of levonorgestrel leading to serious adverse reactions. - Single use of a low dose of LNG is not comparable with the long-term use of hormone preparations, which is associated with the well-known risk of thromboembolism (BfArM). - According to what is currently known, the risk of an ectopic pregnancy is not increased at the onset of pregnancy due to the use of LNG. - LNG does not terminate an existing pregnancy. There is no evidence that ingestion will harm the foetus in the case of an existing pregnancy.
Use (Rx) in Germany	<ul style="list-style-type: none"> - Age distribution of users nationally: <ul style="list-style-type: none"> o According to the German Drug Prescription Report, of approximately 400,000 prescriptions issued annually, only about 50,000 are issued to users under the age of 20 (BfArM); o According to the figures provided by one Bundesland: The age group under 15 years accounted for about 2%, while the age group of 15-16 years for 20%, that of 17-18 years for 37%, and the age group of 19 -20 years for 27% of all prescriptions (EAC expert). - Frequent use as a result of OTC availability is not expected due to menstrual cycle disorders and associated bleeding disorders resulting from frequent ingestion (BfArM).

	<ul style="list-style-type: none"> - Comparison with approved products for the same indication: <ul style="list-style-type: none"> o An EAC expert expressed concerns that if LNG became available OTC but ulipristal remained Rx, patients would rather use LNG for emergency contraception because it is easier to obtain, while he finds that LNG has poor efficacy and is therefore only the second best option; o A centralised Rx-to-OTC switch application for ulipristal emergency contraception is currently pending (BfArM); o For LNG, there are many years of experience available with large numbers of users which is not the case for ulipristal.
International OTC experience	<ul style="list-style-type: none"> - LNG is available OTC in about 80 countries (incl. the US and most European neighbouring countries). - Its main usage is in the age group of 20-24 year olds (EAC expert) - French and British publications do neither show an increase in unprotected intercourse, nor a decrease in the overall use of contraceptives/highly effective contraceptives after the Rx-to-OTC switch. - In countries where emergency contraceptives are available OTC, the rate of abortions have either not declined or have hardly declined at all (BfArM).
Adequacy of product information	<ul style="list-style-type: none"> - The potential low risk of thromboembolism is reasonably reflected in the product information. - The risk of an ectopic pregnancy is sufficiently considered in the product information.
Benefits of OTC availability	<ul style="list-style-type: none"> - Time savings due to OTC availability. However, in the opinion of two experts, the argument of gaining time through faster (i.e. OTC) availability was not so significant. It would be possible for every woman, without an emergency having already occurred, to consult a doctor who could then write a prescription for an emergency contraception.
Advertisement and educational materials	<ul style="list-style-type: none"> - It was suggested to insert/distribute educational materials with the dispensation of LNG. <ul style="list-style-type: none"> o A BfArM representative replied that this is theoretically possible, and implementation in this specific case is to be reviewed. o An advertising ban was discussed, but an EAC expert and a representative of the Ministry of Health explained that pharmaceutical advertising is regulated at EU level and that national amendments to pharmaceutical advertising law is therefore not possible.
Internet sales	<ul style="list-style-type: none"> - It was felt unlikely that a woman concerned would order emergency contraception drugs on the Internet and would rely on order processing and postal delivery to her on the next working day instead of going to the nearest pharmacy (BfArM).

Annex IV



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This article belongs to the Special Issue *The Standing of OTC Medicines in Community Practice*.

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Over-The-Counter (OTC) Drug Consumption Among Adults Living in Germany: Results from the German Health Interview and Examination Survey for Adults 2008–2011 (DEGS1)

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Abstract

In order to assess the effects of prescription-only (Rx) to over-the-counter (OTC) drug switches and related policies, it is imperative to distinguish self-medication from OTC drug use. The objective of this study was to estimate the OTC drug use in the adult population in Germany, to identify its predictors and to highlight methodological differences when compared to the study of a self-medication prevalence. Seven-day prevalence of OTC drug use was calculated on the basis of information provided by 7091 participants of the German Health Interview and Examination Survey for Adults (DEGS1) conducted between 2008 to 2011. Logistic regression analysis was used to identify predictors of OTC drug use. Seven-day prevalence of OTC drug use was higher in women (47.16%) than in men (33.17%). Female gender, an age of more than 60 years, reduced health status, Rx drug use, and multi-morbidity were identified as predictors of OTC drug use. The levels of OTC drug use were higher than the self-medication prevalence found in the same data set probably because some OTC drugs are commonly prescribed by physicians. Drug utilization studies should, therefore, make a methodological distinction between self-medication and OTC drug use depending on whether the focus is on drug safety or the impact of regulatory decisions on the trade status.

Keywords: non-prescription medicines; OTC drugs; self-medication; drug utilization studies; Germany; DEGS1; epidemiology; pharmaceutical public health

Introduction

The use of over-the-counter (OTC) drugs is a subject of high relevance to public health policy. Over past decades, many active ingredients, which previously had been prescription-only (Rx) drugs, have become available OTC [1–3]. At the same time, European health care systems have revised their policies on the reimbursement of OTC drugs [4]. In order to monitor the effects of these policy changes in the general population, it is important to assess the prevalence of OTC drug use and possible predictors thereof.

Apart from a few exceptions, OTC drugs have not been reimbursable by statutory health insurance funds in persons over the age of 12 years in Germany since 2004 [5]. In adults and children over the age of 12 years, the use of OTC drugs can, therefore, not be measured with routinely collected data from statutory health insurance funds. In order to trace the effects of Rx-to-OTC switches and related policies, reimbursement decisions and health policies linked to OTC drugs, it is imperative to distinguish self-medication from OTC drug use and to monitor both types of medication use separately. Despite that fact, all population health surveys representative of the adult population living in Germany have focused on self-medication rather than OTC drug use so far. For instance, the MONICA study of 1990 and the German National Health Interview and Examination Survey of 1998

(GNHIES98) provided seven days of prevalence data about self-medication of 13.1% among 30-year-olds to 64-year-olds and of 34.6% among adults aged 18 to 79 years, respectively [6,7]. In 2013, data on medication use ascertained in the first wave (2008–2011) of the German Health Interview and Examination Survey for Adults (DEGS1) were published [8]. In this study, 58.8% of the population reported use of ‘prescribed preparations’ and 38.8% use of ‘self-medication’ in the previous seven days [8]. ‘Prescribed preparations’ were defined as those prescribed by medical doctors or naturopaths as well as previously prescribed products from family medicine cabinets. ‘Self-medication’ comprised preparations that were self-purchased without a medical prescription in pharmacies, supermarkets, or drugstores as well as drugs from family medicine cabinets that had not been previously prescribed. Differently from the definition of OTC drugs used in our research, self-medication in that study also included “dietary supplements such as vitamins or minerals” [8], medicinal products, and functional foods [8]. The assessment of self-medication in the DEGS1 study and its predecessors relied on information from study participants on how they had obtained the product in question rather than on the official trade status such as Rx status, OTC status, or differentiation from products not considered drugs.

In contrast, little effort has been made to ascertain OTC drug use among German adults. In a 2008 telephone health survey in North Rhine-Westphalia, 38.7% of participants aged 18 years and older reported having used OTC drugs in the previous four weeks [9]. This survey was representative but limited to the population of only one Bundesland (Federal State). A recent attempt to study OTC drug use rather than the self-reported origin of the products was an online-survey carried out in 2013 among 300 German adults, which found a 7-day OTC drug use prevalence of 46.3%. While the study included participants from all over Germany, it cannot be considered representative due to the small sample size and sampling issues inherent to online surveys [10].

The present research study seeks to complement the results of the 2008–2011 DEGS1 [8] and of the online survey from 2013 [10] by analyzing OTC drug use instead of self-medication within the DEGS1 data set. It aimed to provide estimates of the prevalence of OTC drug use within a representative sample of German adults as well as to identify factors influencing their OTC drug use.

Methods

DEGS1, which was conducted by the German Robert Koch Institute between 2008 and 2011, used a two-stage sampling method with examination centers across Germany with the goal of achieving high representativeness of the German population between 18 and 79 years. It consists of standardized, computer-assisted personal interviews (CAPI) on self-reported medical diagnoses and on medicine use, self-administered questionnaires about demographics, self-assessed health, health-

related behavior and well-being, life situation, clinical exams, and laboratory analyses. The study design and sampling method of DEGS1 have been described in depth elsewhere [11–14].

In the invitation letters, the study participants were informed about the objectives and the examination procedures. The study participants received a document about data protection at the examination centers. If they had any questions, they could ask the examination teams at the Robert Koch-Institute or the staff in the examination centers. Participants provided written informed consent prior to the interview and examination.

The present study was based on a sub-sample of the DEGS1 study population, which additionally participated in a standardized CAPI on the use of drugs and dietary supplements [8]. Participants were invited to bring the original packages of all health-related preparations used in the previous seven days and were asked the following question during the CAPI: “Did you use medicines or dietary supplements such as vitamins or minerals during the last seven days? Please also think of painkillers, insulin-containing preparations, injections, and plant-based products. Please also mention preparations from supermarkets or drug stores.” The question was repeated until the participants did not mention any further products. The registration of drugs and other products in the drug use survey was based on the drug registration database AmEDa (Arzneimittel Erfassungs-Datenbank), which is a software product developed by the Robert Koch-Institute drawing on a set of drug master files made available by the Wissenschaftliches Institut der AOK (Scientific institute of the umbrella organization of several German statutory health insurance funds, WIdO) and on the database on dietary supplements of the German National Food Consumption Survey of the MRI, which is the German Federal Research Institute of Nutrition and Food (Max-Rubner Institut). If a product could not be identified with certainty at the study site, a follow-up via mail or telephone was conducted to complete missing information [8]. All persons aged between 18 and 79 years with valid data on the use of drugs and dietary supplements in the last seven days before examination were included in the sub-sample used for the present analysis. Persons who did not take part in the interview on drug usage were excluded. A flowchart on inclusion and exclusion of participants is presented in Figure 1.

For each product, the interviewers scanned the German identification number for pharmaceutical products (Pharmazentralnummer, PZN). Drawing on AmEDa, the software retrieved information on the name, the pharmaceutical company, the pack size, and the pharmaceutical form. Where no PZN was available or information was lacking in the databases provided by WIdO or MRI, the interviewers filled-in the data manually into AmEDa. Further details regarding the design and method of the DEGS1 drug use survey can be found in the following references [8,15]. On the basis of this information, this study differentiated between prescription drugs, OTC drugs, and products were not considered drugs. As reference for the classification of trade status, annex 1 of the Ordinance on

Prescription-Only Medicines (Arzneimittelverschreibungsverordnung, AmVV), which lists all substances subject to Rx status and possible exceptions thereto, was used as the primary source of information. In addition, the drug search engine of the AOK [16], the “Handbuch Rezeptfreie Medikamente” (Handbook of OTC drugs) [5], “Scribas Tabelle” (a German database of Rx drugs) [17], summaries of product characteristics [18], information from manufacturers and vendors, information from online pharmacies and drug stores, and pay-for-access information on vitamin and mineral products compiled by a German foundation for testing/consumer protection (Stiftung Warentest) were used.

For the purpose of this paper, the definition of OTC drugs included both pharmacy-only drugs as well as general sales drugs including products classified as medicines that are available for sale in supermarkets and drug stores. Since these classifications may have been subject to change after and during data collection, coding, and analysis, the legal status as of 15 May, 2016 was considered valid for the products in question. Licensed homeopathic preparations were counted as drugs. Ophthalmologic products were either classified as Rx or OTC drugs. If study participants mentioned active ingredients/drug names/brands that could be either Rx or OTC drugs, the drugs were classified according to how participants reported having obtained them. If study participants mentioned active ingredients/product names/brands that could be either OTC drugs or dietary supplements, these entries were randomly assigned to either one or the other, according to the share of OTC drugs and dietary supplements of that specific active ingredient/drug name/brand on the German market. The latter information was obtained from pertinent pharmaceutical companies or vendors. If participants mentioned active ingredients that could be Rx drugs, OTC drugs, or dietary supplements and did not provide further specifications such as brand name or pharmaceutical form, such entries were classified as missing variables even if participants mentioned how they had obtained the product.

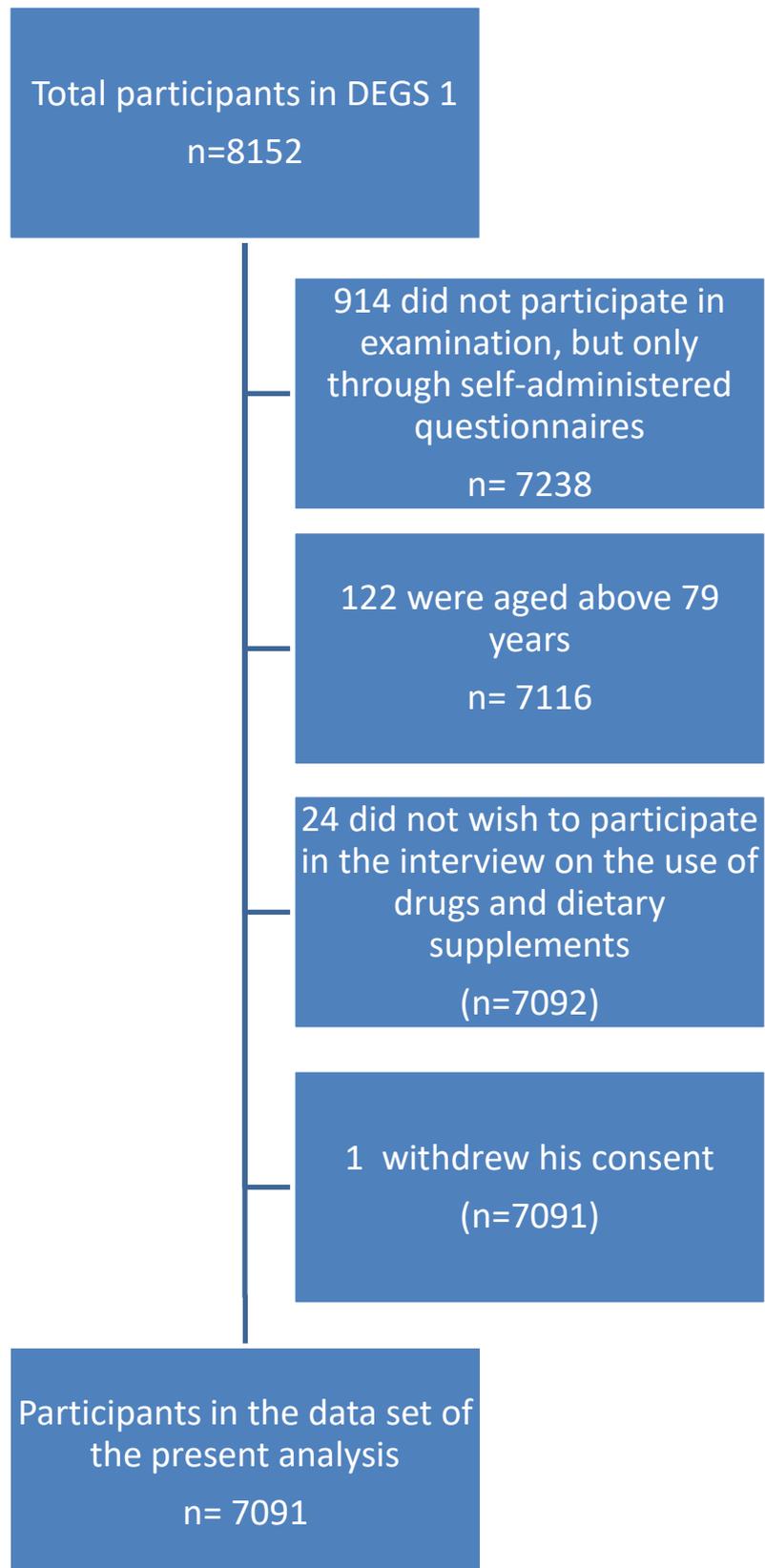


Figure 1: Flowchart of inclusion and exclusion of study participants.

As possible predictors for OTC drug use, education, net household income, migration status, type of health insurance, urbanization, socio-economic status, self-reported health, multi-morbidity, mental health disorders, alcohol consumption, and Rx drug use in the previous seven days were considered. The selection of possible predictors was partly based on finding from other studies on factors correlated with or predictors of OTC drug use and self-medication and partly on the authors' own hypotheses. Information on education, household income, migration status, type of health insurance, and self-reported health was obtained from questionnaires filled in by the participants themselves. The reported highest level of education was classified based on the International Standard Classification of Education 1997 as defined by UNESCO and assigned to the categories "low," "medium," and "high," according to the German micro-census categories [19,20]. For the level of urbanization, a distinction was made between "rural" (<5000 inhabitants), "small town" (5000–<20,000 inhabitants), "medium-sized town" (20,000–<100,000 inhabitants), and "city" (≥100,000 inhabitants). The classification of socio-economic status (SES) was based on education, profession, and household income [21]. The questionnaire also enquired whether participants or their parents were born abroad. On that basis, migration status was determined according to three categories classified as "none," "one parent," and "both parents." People who were born abroad counted towards the latter category [22]. In the same questionnaire, participants were asked to provide information about their health insurance arrangements. This information was then classified into the three categories "statutory health insurance," "private health insurance or health care scheme for civil servants (Beihilfe)," and "other" by the DEGS study team. Information on self-reported health statuses was based on the question "How is your health status in general?" with the answering options "very good," "good," "moderate," "poor," and "very poor."

In order to study multi-morbidity as a possible predictor of OTC drug use, information on health conditions and diseases was obtained through a physician-administered CAPI. For the purpose of our study, 'multimorbidity' [23,24] was defined as the presence of two or more of the following conditions: *in the last twelve months presence of* self-reported physician-diagnosed hypertension, coronary heart disease, cardiac insufficiency, diabetes, dyslipidaemia, circulatory disorders of the legs, asthma, thyroid disease, gastroduodenal ulcer, hepatitis, chronic inflammatory bowel disease, gout, rheumatoid arthritis, migraine, epilepsy, hay fever/allergic rhinitis, and neurodermatitis; *current medical care for* cancer, *ever diagnosed with* chronic renal insufficiency, arthrosis/degenerative joint disorders, osteoporosis, or Parkinson's disease. A variable on mental health disorders was based on participants' reports of the presence of one or more of the following physician-diagnosed illnesses: eating disorders, anxiety disorders, depression, and burn-out syndrome. The alcohol consumption was assessed using the AUDIT-C methodology and the results were classified into the categories "never," "moderate," and "risk behavior" [25].

To account for differences in terms of age, gender, region, citizenship, urbanization, and education between the study sample and the general German population between 18 and 79 years (as of 31.12.2010) as well as for the two-staged sampling approach, which is a weighting factor introduced for the DEGS1 study [15]. Percentages and means were calculated taking this weighting factor into account using the survey procedure of Stata. Possible predictors of OTC drug use were studied through logistic regression analysis using a manual forward approach. The order of possible independent variables to be included in the logistic regression model was based on results from unadjusted Student t-tests and chi-square tests at the sample level including those variables with the highest significance level first. Variables with equally low p -values of $p < 0.000$ found in the unadjusted tests for inference were included in the following order: gender, age, urbanization, self-reported health, multi-morbidity, and mental health disorders.

For the logistic regression analysis, the above-mentioned weighting factor was applied throughout by using the Stata survey procedure to ensure the results are valid at the population level. To assess goodness-of-fit of the respective models at each stage of model building, the Archer and Lemeshow F -adjusted mean residual test for binary logistic regression models fitted to survey data [26,27] was used through the post-estimation *estat gof* command of Stata. An increase in goodness-of-fit was used as an inclusion criterion for the variables. For the Archer and Lemeshow F -adjusted mean residual test, a p -value of <0.05 indicates a lack of fit. For means and odds ratios, a p -value of <0.05 or a lack of overlap of 95% confidence intervals were considered indicative of statistical significance. All statistical analyses were conducted with Stata 13.

Results

Study population

Out of 7116 participants aged 18 to 79 years who took part in the physical examination of DEGS1, 7091 also participated in the interview on the use of drugs and dietary supplements. Their demographic characteristics are summarized in Table 1.

Table 1: Study population

Gender	n	Weighted Percentage
Male	3399	49.7
Female	3692	50.3
Age groups		
18–29	1065	18.8
30–39	838	14.7
40–49	1293	21.5
50–59	1394	18.2

60–69	1393	14.1
70–79	1108	12.7
Urbanization		
Rural (<5000 inhabitants)	1301	15.3
Small town (5000–<20,000 inhabitants)	1711	24.0
Medium-sized town (20,000–<100,000 inhabitants)	2069	29.3
City (≥100,000 inhabitants)	2010	31.4
Self-reported health status		
Very good	909	14.2
Good	4300	60.5
Moderate	1646	22.7
Poor	173	2.3
Very poor	22	0.3
Migration status		
None	5854	80.1
One parent	311	4.8
Both parents	699	15.1
Socio-economic status		
Low	1129	19.6
Medium	4246	60.4
High	1672	19.9
Education		
Low	1003	21.1
Medium	3773	55.1
High	2271	23.7
Net household income (Euros)		
≤1500	2030	29.1
>1500 ≤2500	2388	33.2
>2500 ≤3500	1406	20.2
>3500 ≤4500	661	9.2
>4500 ≤5500	355	4.7
>5500	251	3.5
Type of health insurance		
Statutory health insurance	6055	87.7
Private health insurance or health care scheme for civil servants (Beihilfe)	841	11.6
Other	49	0.8
Multimorbidity		
Yes	2467	30.8
No	4624	69.2
Mental health disorders		
Yes	506	7.7
No	6585	92.3
Alcohol consumption		
Never	777	13.0
Moderate	3794	53.7
Risk behaviour	2252	33.4

Drug Use Prevalence

The 7-day prevalence of having used at least one OTC drug was 40.2% in total and 33.2% and 47.2% for men and women, respectively. For the use of at least one Rx drug, the seven-day prevalence was 45.4% among men, 69.7% among women, and 57.6% among the total population. Regarding the dietary supplements, their use in the previous seven days was found to be 11.0% of men, 20.4% of women, and in 15.7% of the total population. The mean numbers of OTC drugs used in the past seven days in both genders was 0.67 (95% CI: 0.63–0.71), 0.47 (95% CI: 0.43–0.50) in men, and 0.87 (95% CI: 0.81–0.93) in women. The gender difference was statistically significant. An overview of the seven-day prevalence per number of drugs used is provided in Table 2.

Factors Associated with OTC Drug Use

All variables presented in Table 1 were considered for inclusion in a logistic regression model. The best-fit model found the following statistically significant predictors for the use of at least one OTC drug in the previous seven days: female gender, multimorbidity, good, moderate, poor, and very poor self-reported health in comparison to very good self-reported health, ages 60–69, and 70–79 years, and Rx drug used in the previous seven days (see Table 3).

The F-adjusted mean residual test statistic of the presented model was 0.25 ($p = 0.9869$). Urbanization, alcohol consumption, and mental health disorders were not included in the final model since these variables lowered the goodness-of-fit. Household income was included in the model rather than education status or socio-economic status since it made, in comparison, the greatest contribution to goodness-of-fit.

Table 2 Seven-day prevalence of use of OTC drugs, Rx drugs, and dietary supplements per number of products used.

	Number of Products	OTC Drugs			Rx Drugs			Dietary Supplements			
		n	Prevalence (Weighted Percentage)	Weighted Mean (95% CI)	n	Prevalence (Weighted Percentage)	Weighted Mean (95% CI)	n	Prevalence (Weighted Percentage)	Weighted Mean (95% CI)	
Men	0	2195	66.8	0.47 (0.43–0.50)	1643	54.5	1.18 (1.10–1.26)	2964	88.9	0.15 (0.13–0.18)	
	1	853	24.1		560	16.6		326	8.5		
	2	226	5.9		374	9.8		68	1.5		
	3	87	2.4		281	7.1		23	0.4		
	4	21	0.5		232	5.4		10	0.4		
	≥5	17	0.3		309	6.6		8	0.1		
Women	0	1911	52.7	0.87 (0.81–0.93)	1045	30.1	1.66 (1.59–1.74)	2874	79.5	0.30 (0.27–0.33)	
	1	1013	27.0		1044	29.6		558	14.1		
	2	427	11.7		635	16.9		174	4.5		
	3	191	4.8		367	9.1		57	1.3		
	4	62	1.5		245	5.7		18	0.4		
	≥5	88	2.2		356	8.5		11	0.1		
Total	0	4106	59.7	0.67 (0.63–0.71)	2688	42.2	1.42 (1.36–1.48)	5838	84.2	0.23 (0.21–0.25)	
	1	1866	25.6		1604	23.1		884	11.3		
	2	653	8.8		1009	13.3		242	3.0		
	3	278	3.6		648	8.1		80	0.9		
	4	83	1.0		477	5.5		28	0.4		
								7.6			
	≥5	105	1.2		665			19	0.1		

Table 3: Factors associated with OTC drug use in the previous seven days among German adults aged 18–79 years.

Predictors for Using at Least One OTC Drug	OR	95% CI	<i>p</i>
Gender			
Male	Reference		
Female	1.64	1.44–1.86	<0.001
Age group (years)			
18–29	Reference		
30–39	1.10	0.86–1.40	0.438
40–49	1.17	0.94–1.45	0.154
50–59	1.11	0.89–1.38	0.346
60–69	1.59	1.27–1.98	<0.001
70–79	2.14	1.69–2.71	<0.001
Self-reported health			
Very good	Reference		
Good	1.50	1.21–1.86	<0.001
Moderate	2.14	1.69–2.75	<0.001
Poor	1.75	1.10–2.80	0.020
Very poor	4.16	1.03–16.84	0.046
Multimorbidity			
No	Reference		
Yes	1.52	1.29–1.79	<0.001
Household income (Euros)			
≤1500	Reference		
>1500 ≤2500	1.05	0.90–1.24	0.541
>2500 ≤3500	1.26	1.06–1.51	0.010
>3500 ≤4500	1.14	0.87–1.50	0.352
>4500 ≤5500	1.36	0.97–1.91	0.078
>5500	1.22	0.85–1.76	0.277
Migration status			
None	Reference		
One parent	0.80	0.57–1.11	0.173
Both parents	0.90	0.71–1.14	0.391
Rx drug use			
No Rx drug use in the previous seven days	Reference		
Rx drug use in the previous seven days	1.30	1.11–1.51	0.001
Constant: OR: 0.1882222 <i>p</i> < 0.001			
Goodness-of-fit test: <i>F</i> (9, 171) = 0.25, <i>p</i> = 0.9869			

Discussion

Our study examined for the first time OTC drug use in a representative sample of the adult population living in Germany. We found a seven-day OTC drug use prevalence of 40.2%. Female gender, older age, reduced self-reported health status, and multi-morbidity were significant predictors of OTC drug use among that population.

The finding of a seven-day OTC drug use prevalence of 40.2% was unexpected, as Knopf et al. had, based on the same data set and the broader definition of ‘self-medication’ instead of ‘OTC drug use’,

only found a seven-day self-medication prevalence of 38.8% [8]. In order to better understand these findings, the differences in the methods of the two studies require a closer look. In both cases, data were collected by asking participants whether they had used medicines or other health-related products during the last seven days including preparations from supermarkets or drug stores. For the purpose of our study, additional information on PZN, name, pharmaceutical company, pack size, and pharmaceutical form was then used to determine the trade status of the respective product, which is defined as whether the product was an Rx drug, an OTC drug, or no drug at all. Knopf et al., in turn, did not classify the drugs into Rx drugs and self-medication according to their trade status but relied on information by study participants on how they had obtained the products. For this classification, participants could specify one of the following options: (i) prescribed by a physician, (ii) recommended by a naturopath, (iii) bought without a prescription, (iv) from the family medicine cabinet previously bought without a prescription, (v) from the family medicine cabinet previously prescribed, (vi) other, and (vii) unknown. When analyzing the seven-day prevalence of self-medication, Knopf et al., therefore, summarized categories (iii) and (iv) into the category of self-medication regardless of the actual trade status of the products mentioned in these categories. The assumption that self-medication as such includes a larger variety of products than OTC drug use since it also includes dietary supplements and other product falls, however, short of the fact that there may be drugs and homeopathic products that are generally prescribed or recommended by physicians or naturopaths, they have OTC status. We believe that these methodological differences in classifying OTC or self-medication use explain the discrepant and unexpected results based on the same data set.

For the purpose of this study, homeopathic preparations were classified as either Rx or OTC drugs depending on the dose (homeopathic potentisation), according to annex 1 of the AmVV. However, homeopathic preparations were not counted towards self-medication by Knopf et al. if they had been recommended by naturopaths. Among the DEGS1 study population, 1.6% used products recommended to them by naturopaths. In the majority of cases, these are OTC products since naturopaths cannot prescribe Rx products unless they are also licensed physicians.

The discrepant results between this study and the study by Knopf et al. could also be due to drugs that are OTC in terms of their trade status but are, nonetheless, commonly prescribed by physicians. In the DEGS1 study population, 16.7% of participants had used at least one OTC drug in the previous seven days that had been prescribed or recommended by a physician. For example, it is likely that low-dose acetylsalicylic acid (ASA) was often “prescribed by a physician” and, therefore, did not qualify for the classification of “self-medication,” according to the categories defined by Knopf et al. However, low-dose ASA is an OTC drug, according to its trade status. ASA in a dose of up to 300 mg

can be reimbursed by statutory health insurance funds in patients with stable coronary heart disease or following myocardial infarction or stroke despite its OTC status [5,28] resulting in higher physician prescribing of this OTC drug. Despite the generally low price per pack, which can occasionally be below the supplementary payment for prescription drugs, a significant amount of low-dose ASA is still prescribed. According to the German Drug Prescription Report (Arzneiverordnungs-Report) from 2012, 618.8 million defined daily doses of low-dose ASA were prescribed and charged to statutory health insurance funds in 2011, which is the last year of the data collection phase of the DEGS1 study [29].

Despite the seemingly little difference between the self-medication and OTC drug use prevalence and the possible explanations for this finding presented above, a 40.2% OTC drug use prevalence presents an important result in German pharmacoepidemiologic research and has implications for the greater public health context. For example, because only due to the methodological distinction, we were able to show that OTC drug use concerns a significant part of the population while it would also have been conceivable to find a much lower prevalence of OTC drugs used compared to that of self-medication, which may actually be the case in other countries. However, considering that the policy is made on the basis of different trade statuses rather relying on a distinction of self-medication from non-self-medication and that OTC drug use in the population is significant, our work supports the argument that OTC drug use should receive more attention in public health policy, which is currently rather limited.

The analysis of the number of products used suggests that polypharmacy with OTC drugs does not seem to present a major concern since the majority of OTC drug users limit their consumption to one product within a seven-day time frame.

OTC drug use was significantly higher among people aged 60 years and older. Moreover, multi-morbidity was identified as a significant predictor for OTC drug use. While most diseases and conditions included in our definition of multi-morbidity require treatment with prescription drugs, there are also OTC options for some of them in Germany. For example, there are OTC drugs for the treatment of coronary heart disease, circulatory leg disorders, gastroduodenal ulcers, and hay fever/allergic rhinitis such as low dose ASA, proton pump inhibitors, or second-generation antihistamines [5]. Both older people and those affected by multi-morbidity may represent vulnerable population groups with regard to OTC drug use, which is seen by contraindications or precautions and warnings that refer to certain age groups or conditions and diseases, which can be found in the summary of product characteristics of several OTC drugs [3]. Therefore, the finding of our study that multimorbidity and higher age are predictors of OTC drug use is of high relevance to regulators making decisions on Rx-to-OTC switches. To date, there is no specific guidance on Rx-to-

OTC switches in Germany. However, acknowledging the significant share of OTC drug users in the population, it would be advisable that such policies were developed in the form of criteria guiding the German Expert Advisory Committee on Prescription-Only Issues in its deliberations when advising on switch applications. Such criteria should then also include considerations regarding a higher age and multi-morbidity to ensure that risks from OTC drug use for the population will be adequately assessed.

OTC drug use was also significantly higher in any self-reported health category that was worse than “very good.” This finding contradicts that of a Spanish study, which found significantly higher levels of self-medicated analgesic use among adults with good or excellent health status [30]. However, it is well-known that the measure of self-reported health is subject to important cultural influences and unadjusted cross-country comparisons are, therefore, difficult to make [31].

Drug use was generally significantly higher among women with regard to OTC drugs, Rx drugs, and dietary supplements, which are in line with previous findings from Germany and elsewhere [4,6–9]. Income, education, and SES were studied separately as possible predictors for OTC drug use because SES is a variable composed of education, income, and professional status. We did not identify income as a significant predictor for OTC drug use but the variable made a more powerful contribution to the goodness-of-fit of the logistic regression model than the other variables. This finding is quite important since an association between higher SES and self-medication has been reported in studies from Germany before [7,9] while no association between education and OTC drug use has been found [10]. It is conceivable that there is an association between income and OTC drug use for which the finding of the OR of 1.26 (95% CI: 1.06–1.51, $p = 0.01$) for a household income of $<2500 \leq 3500$ Euros, which may also be considered indicative, but that it could not be shown in our model due to the application of the linearizing weighting factor. It would be desirable to better understand the respective influence of professional status, education, and income on OTC drug use and their implications for public health policy and practice with regard to safe use, compliance, oversupply, and equitable access. For instance, it may be the case that people who are able to afford OTC drugs are using more than necessary while others are unable to afford an OTC drug despite a medical need.

Similar to the association with income, education, and SES, urbanization as a proxy for easier access to OTC drugs did not add to the goodness-of-fit of the logistic regression model, but it may be worthwhile to study other possible proxy measures for accessibility such as purchasing OTC drugs over the internet and whether such purchases are related to higher OTC drug use as well as whether easier accessibility of OTC drugs affects their safe use. Rx drug use in the previous seven days was identified as a significant predictor of OTC drug use. This finding is in line with that of an online survey on OTC drug use in Germany [10]. A statistically significant association between OTC drug use

and alcohol consumption was found at the sample level, but, when included into the logistical regression model, alcohol consumption neither added to the goodness-of-fit of the model nor were the odds ratios statistically significant after applying the linearizing weighting factor. The variable was therefore not included into the final logistic regression model. The question of whether there is an association between OTC drug use and alcohol consumption may nonetheless merit further attention in future studies, but it is unclear whether such an association had any implications for clinical or regulatory practice. In a review article by Prescott, for instance, it was shown that there is no evidence of acute hepatotoxic incidents following paracetamol use at therapeutic dosages in alcoholics [32].

As with previous population-based German studies on drug use [6,7,33,34], the DEGS1 survey was intended to study self-medication and prescribed medication. While it is often desirable to use harmonized methodologies in drug utilization studies to enable comparisons across different times and locations, using different methodological approaches may provide new perspectives by emphasizing other aspects of drug use. The approach of studying the use of self-medication versus prescribed/recommended medication based on prescription or recommendation vs. self-purchase as pursued by Knopf et al. is particularly useful when questions of OTC drug safety are of concern. In such cases, the question of whether patients received instructions from their physicians rather than the trade status of the drug of concern will play an important role. The classification approach of OTC and Rx drugs based on their trade status, in turn, can inform or support the evaluation of changes to drug law since changes to trade status are made along the lines of legal distinctions between Rx status, OTC status, and their delineation from non-drugs. Considering the complexities of the OTC drug market and the different products and therapeutical categories, it is obvious that an evaluation of an actual Rx-to-OTC switch or another substance-specific regulatory decision would require studying the epidemiology of that particular drug or group of drugs. However, the analysis of OTC drug use as seen in the present study can provide guidance for the regulation of the legal category of OTC drugs such as deciding what considerations need to be made for assessing applications to changing drug trade statuses.

Regularly conducted population health surveys present a unique opportunity for monitoring OTC drug use, which cannot be measured by routine data from statutory health insurance funds. Moreover, the DEGS1 data set also includes –to a limited extent– information on medication not being part of the formal German drug market. However, it was beyond the scope and the technical and financial possibilities of this study to estimate the prevalence and predictors of inappropriate drug use. However, it would be desirable to focus on these topics in future research in the field of OTC drugs.

While the specific usage patterns and regulations concerning OTC drugs are unique to each country, this study adds value to international pharmaceutical public health through the general methodological insight that self-medication and OTC drug use are not equivalent concepts and that, empirically, a corresponding population prevalence may differ.

Strengths and Limitations

The present study has several strengths such as relying on the elaborate design and the large sample size of the DEGS1 survey, which is representative of the adult population in Germany. A limitation, however, is the upper age limit of 79 years in the study population. Since we could show a strong correlation between OTC drug use and higher age, it is likely that the true effect has been underestimated in this study. Similarly, we identified multi-morbidity as an important predictor for OTC drug use but the true effect may be larger than reported here since patients with multi-morbidity may be affected by reduced mobility and, therefore, may have been unable to travel to DEGS study sites. However, the high level of the goodness-of-fit of the logistic regression model shows that, overall, the predictors of OTC drug use have been selected appropriately.

Another positive feature of the DEGS1 survey is that information about drugs used in the previous seven days was collected in CAPI interviews. Furthermore, participants were invited to bring the packages of the drugs used to the interview where they could be scanned, which allows for semi-automatized collection of data. By scanning the packages, the relevant information including was provided for 73% of the preparations while 27% had to be subsequently researched and manually entered [8]. A limitation is that the DEGS1 survey questionnaire contained a filter variable asking whether a drug was used regularly or occasionally. During CAPI interviews of DEGS1, further questions about the actual use of drugs were only asked if they were used regularly [35]. That, however, is not a common feature of OTC drug use [3,36] and, thereby, prevented a more in-depth analysis of OTC drug use.

Despite a greater completeness of the medication data collected at the study sites, telephone and mail follow-up was conducted for 1.5% of the participants [8] to ensure even greater completeness of the information on drugs used, which presents a strength of this study. However, whether a product used had Rx or OTC status was not directly recorded. Nevertheless, in the context of our study, the trade status of each product was carefully assessed on the basis of various information sources. This permitted the differentiation of OTC and Rx drug use and the subsequent analysis of OTC drug use which previously could not be done.

Conclusions

Drug utilization studies should not consider 'self-medication' and 'OTC drug use' as synonyms. Rather, both concepts should be monitored separately depending on the aim of the health policies they seek to inform. For example, the question of how patients obtained certain drugs is different from how legal provisions on trade status translate into drug consumption patterns in practice. While the former question can improve the evidence base for questions of drug safety where the interaction with a physician is pertinent, the latter can help assess the impact of regulatory decisions on trade status. Distinguishing self-medication and OTC drug use in research of public health practice is, therefore, not trivial. Moreover, significant amounts of OTC drugs may actually be prescribed or recommended by physicians, which merits further scientific attention.

With a 40.2% prevalence of OTC drug use, the latter makes a substantial contribution to the pharmaceutical supply in Germany and the safe use of OTC drugs should, therefore, receive the attention in public health research and sanitary consumer protection it deserves. However, OTC drug use is rarely the focus of drug utilization studies. It should be also considered that opportunities to study OTC drug use are more limited than those utilized for studying Rx drug use. In order to enhance the scarce empirical evidence on OTC drug use in Germany with future population-based studies, it would be valuable to amend the drug use survey questionnaire by including the legal status of drugs and by collecting further information on drugs used only occasionally. Collecting both types of information would permit specific analyses depending on the health policy question they seek to inform.

With odds ratios of 1.6 and above, female gender, an age of 60 years and older, a moderate, poor, and very poor health status were the five strongest predictors for OTC drug use. These findings can be useful in developing regulatory guidance on Rx-to-OTC switch decisions. In addition, the associations between older ages and multi-morbidity and OTC drug use should be considered in future policy decisions on OTC drugs in Germany.

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