from new molecules to leads for innovation

studies on the post-innovation learning cycle for pharmaceuticals

pieter stolk

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Van nieuwe moleculen tot aanwijzingen voor innovatie – Studies aan de post-innovatie leercyclus voor geneesmiddelen
(met een samenvatting in het Nederlands)

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contents

General introduction

chapter 1

chapter

BACKGROUND

The pharmaceutical arena is evolving constantly: new drugs enter the market while older ones are discontinued, clinical practice changes, health care budgets rise and fall, and public health needs are redefined. Against this background, the achievement of three main policy goals related to pharmaceuticals has to be monitored continuously:[1]

1. To ensure patient access to safe and effective medicines that are used in the context of a high quality delivery system;
2. To allocate scarce resources in a health system in such a way that pharmaceutical spending remains sustainable, while optimal health outcomes for the individual patient are achieved;
3. To create an environment where innovation is rewarded, and the aims of (national) industrial policies are achieved.

The ways in which societies reconcile these three goals are manifold, leading to a variety of health systems, allocation policies, and usage patterns.[2-5] Currently, several important issues have converged that pose important challenges to the fulfilment of the main policy goals. For example, there are growing concerns about the ability of the current system to satisfactorily respond to issues surrounding drug safety. This may lead to a decrease in the trust that patients and health professionals have in the health system as a vehicle to deliver high quality care.[6,7] Furthermore, governments are faced with growing health care expenditures due to demographic developments and the increasing per unit treatment costs of new drugs.[8] This leads to strong incentives for cost containment. Also, the number of innovative drugs coming to the market is decreasing and profit margins for companies are under pressure, which will change the structure of the industry in the coming years.[9,10] Although the precise extent or source of the dearth of drug innovation is unknown, changing regulatory requirements may be a key issue.[11] Moreover, there is a continuing discussion about whether or not innovation is matched to real public health needs. This was analysed in detail in the 2004 report of the World Health Organisation (WHO) 'Priority medicines for Europe and the world'.[12] The mismatch not only relates to diseases that are highly prevalent in low- and middle-income countries, but also to diseases that affect patients around the world (e.g. Alzheimer's disease, stroke and the orphan diseases).

Between these challenges that confront regulators worldwide there are many cross-links: interventions to address one issue often have a broader impact as well. An example for this can be found in a recent retrospective cohort study of patients with acute coronary syndrome, discharged from hospital and receiving posthospital treatment with clopidogrel (Plavix®), an antiplatelet drug. In the study, an increase in mortality in the first 90 days after the discontinuation of clopidogrel was found.[13] Because of the high costs of clopidogrel compared to alternatives such as acetyl salicylic acid, this drug has been a frequent target for cost containment interventions by regulators and third party payers. Therefore, reimbursement policies may have played a role in determining the duration of use for individual patients. One of the authors of the study, Dr. John Rumsfeld, remarked: "Cost must be an issue here. If clopidogrel cost the same amount as aspirin, perhaps we would be recommending indefinite use of this drug as well."[14]

This example shows that careful assessment of the possible impact of regulatory intervention on the usage environment is warranted. Ideally, proposals for policy changes should be backed up by information about current use or the impact of prior interventions. In his evaluation of regulatory requirements during the development phase, Rawlins has proposed two criteria to evaluate all regulations:[15] is there a clear evidence-base to support the continuing of the regulation? And, does each regulatory requirement offer value for money? To answer these questions in a satisfactory way, information from the usage environment is needed.[16]

Furthermore, data form the usage environment can also provide important information and incentives for drug development and innovation. The study on the clinical impact of the discontinuation of clopidogrel described above is such an example. New insights from drug use in clinical practice is one of the three main routes for 'post-innovation innovation': the discovery of new indications after market entry.[17] In this way, insights from use in clinical practice, for example through pharmacoepidemiological studies, can contribute to the learn-confirm cycle of drug development.[18]

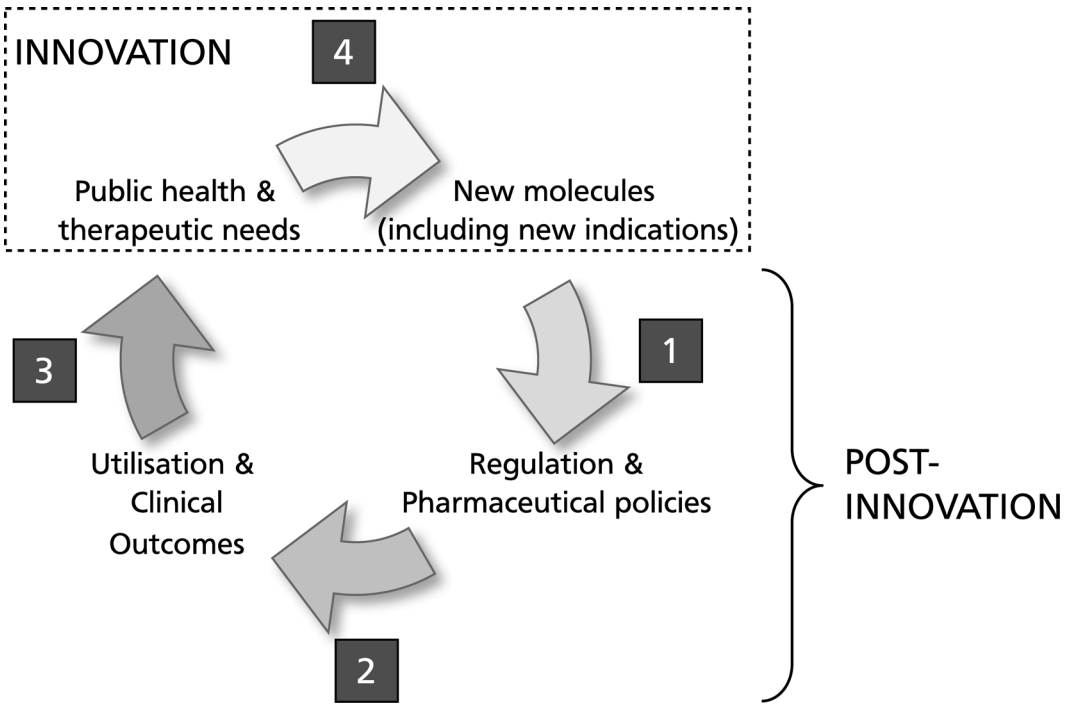
To assist in thinking about the usage environment of drugs in a comprehensive manner that includes regulation, clinical outcomes, and incentives for innovation, we propose a conceptual learning cycle for pharmaceuticals that incorporates all these elements. Results from studies on this learning cycle can be

helpful in designing future policies, as well as identifying opportunities for optimising drug use and the innovation process.

THE LEARNING-CYCLE FOR PHARMACEUTICALS – A CONCEPTUAL FRAMEWORK

The cycle that we want to use as the conceptual framework is described in Figure 1. The framework contains a 'pre-innovation' phase and a 'post-innovation' phase. The distinction between innovation and post-innovation is based on the work of David Banta, who places the moment of 'innovation' at the start of clinical use.[19] In this thesis we want to focus on the 'post-innovation' part of the cycle that begins with the embedding of a new drug in the existing health care system, and ends with the leads for innovation that arise from use in clinical practice.

FIGURE 1 - A proposed learning cycle for pharmaceuticals



The first step in the cycle is when a drug receives a market authorisation by a regulator such as the European Medicines Agency (EMEA) or the US Food and Drug Administration (FDA) (*Section 1*). At this moment, the new drug or drug class must be embedded in the existing regulatory and health system. For example, payers have to make a decision about whether or not the drug should be reimbursed, and professional organisations have to make a decision about the role of a drug in clinical practice.

In the next section of the cycle, the drug is taken up and used in clinical practice by patients and health professionals (*Section 2*). During this period, more information comes available about the benefits and risks of the new drug. Use in clinical practice is heavily influenced by reimbursement policies and guidelines.

Based on the position that the drug attains in clinical practice and the outcomes of drug treatment, the therapeutic needs of the population may change or leads for new indications or future drugs are discovered; both of these provide incentives for pharmaceutical research and development (*Section 3*) .

Next, we come to the drug development (pre-innovation) phase of the cycle (*Section 4*). This section contains all drug discovery and clinical development within academia and industry, including all pre-marketing activities of regulators such as FDA, the EMEA and national authorities. Ideally, the product of this process is marketed as a new drug, returning us to *Section 1* of the learning cycle.

In this thesis we will use a variety of analysis tools to study the links between the first three sections of the learning cycle for pharmaceuticals, the phase for post-innovation learning. We will evaluate how these tools can best be used and adapted for this purpose. The tools used in this thesis include pharmacoepidemiological methods, multicountry comparisons and case studies. We are especially interested in the international context, making use of the natural variability of policy environments and health care systems.

POST-INNOVATION LEARNING FOR PHARMACEUTICALS (PILLS) - OBJECTIVES OF THIS THESIS

A primary objective of this thesis is to develop a set of analytical tools to study the post-innovation learning cycle of pharmaceuticals. With these tools we aim to provide an evidence base for the formulation of policies that want to achieve a

sustainable balance between providing good quality health care, stimulating the optimal allocation of scarce resources, and fostering an environment where innovation is adjusted to real public health needs. Finally, we want to identify directions for future research.

OUTLINE OF THIS THESIS

This thesis contains nine studies divided in three chapters. Each chapter is located on a section of the post-innovation learning cycle presented in Figure 1.

In **Chapter 2** we will focus on several challenges for policymakers that arise from specific characteristics of new molecules, *Section 1* in the cycle. An example that we will study is the Defined Daily Dose (DDD), which plays an important role in the price-setting systems of many countries. Also, we will explore the implications of new therapeutic groups for policies of global organisations such as the WHO. Finally we look at how the use of orphan drugs varies in different EU member states.

Chapter 3 focuses on the relationship between regulation and use in clinical practice, represented by *Section 2* in the cycle. Firstly, we look at a policy interventions at the micro level: the discontinuation of the reimbursement of oral contraceptives. In the second study we use a macro perspective by looking at the relationship between guideline preferences and the use of antihypertensives in clinical practice in a multicountry setting. Another macro level study looks at clopidogrel (Plavix®), an expensive antithrombotic drug that poses special challenges to the payers in the health system. Here we look at the differences between the EMEA market authorisation, the national reimbursement conditions and actual use in nine EU member states. Finally, we use a life-cycle perspective to look at how signals from the usage environment are translated into a regulatory response for two drug safety cases, the market withdrawal of cerivastatin (Lipobay®) and the safety issues surrounding suicide and Selective Serotonin Inhibitors (SSRIs) in children.

In **Chapter 4** we present two studies that show how information from actual use in clinical practice can provide leads for drug development, the third section in the cycle. We concentrate on the field of psychiatry and two classes of drugs that have been linked to possible beneficial effects in patients with severe psychiatric

illness: cyclooxygenase-2 (COX-2) inhibitors in schizophrenia, and non-steroidal anti-inflammatory drugs (NSAIDs) in bipolar disorder.

In **Chapter 5** the results from the earlier chapters are discussed in the context of the post-innovation learning cycle and, based on this, we will provide a synthesis and directions for future research.

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Embedding new drugs in the health system

chapter 2

chapter

chapter 2.1

Changes in the defined daily dose: CYP2D6/CYP3A metabolism as an indicator for dose setting problems

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ABSTRACT

Objective

Interindividual variability is common at all stages of drug absorption, distribution, pharmacodynamics, metabolism and elimination. In this study, we focused on two enzymes involved in phase-I drug metabolism as markers of pharmacological variability: the CYP3A and CYP2D6 subsystems of cytochrome P450. The main aim of our study was to determine whether substrate drugs for CYP2D6 and/or CYP3A enzymes, showing high interindividual metabolic variability, are more prone to post-marketing adjustments of defined daily dose (DDD).

Methods

A case-control design was used. We identified all DDD changes between 1982 and May 2004 through the website of the World Health Organisation Collaborating Centre for Drug Statistics Methodology. Cases were drugs with a DDD change and controls were other drugs with unchanged DDDs. Information about metabolism pathway, introduction year, literature exposure and administration route was retrieved.

Results

We included 88 cases and 176 controls. Of the 88 cases, 51 were dosage decreases (58.0%). Overall, DDD changes were not associated with CYP2D6/CYP3A metabolism (odds ratio [OR] 1.92; 95% confidence interval [95%CI] 0.78–4.72). However, DDD decreases were associated with CYP2D6/CYP3A metabolism (OR 3.21; 95%CI 1.25–8.26). Adjusting for introduction year weakened this effect (OR 2.78; 95%CI 0.98–7.90).

Conclusion

Our study indicates that CYP2D6 and CYP3A substrates are more likely to require a DDD decrease after granting of market authorisation. However, this effect was diminished by adjusting for period of introduction. The implication of this finding is that variability indicators, as is demonstrated in this study for CYP2D6/CYP3A metabolism, can exert their influence on a wide variety of drug measures, such as the DDD.

INTRODUCTION

Various authors have stressed the provisional nature of assessments about effectiveness and safety of medicines at the time when a new active substance is introduced into clinical practice.[1,2] The same holds for finding the right dose on the basis of pre-authorisation studies.[3,4]

Dosing of pharmaceuticals is a dynamic process, in which recommended dosages may undergo changes over time. When Cross et al. studied labelling changes of New Molecular Entities in the United States approved by the Food and Drug Administration between 1980 and 1999, they found that one in five compounds underwent a dosage change after marketing.[3] Our group has previously reported on 115 changes in the defined daily dose (DDD) – a dose measure developed and maintained by the World Health Organisation (WHO) – and came basically to the same conclusion.[4] DDD increases were most frequently associated with antibiotics, while cardiovascular drugs underwent more dose decreases. An important finding from both studies was that newer drugs were more susceptible to post-marketing dose changes than older drugs.[3,4]

Thus, optimising dosage strategies remains an important challenge for drug development.[5] Causes for dosage changes may be found anywhere in the drug life-cycle. Both pharmaceutical, clinical and economical determinants of variability in dosing have been reported.[6,7] A classic example is the post-marketing dose reduction of captopril, where the initially recommended dose was much higher than necessary for the vast majority of patients being prescribed the drug in routine clinical practice.[8]

In pharmacology, interindividual variability is common at all stages of drug absorption, distribution, pharmacodynamics, metabolism and elimination. For metabolism, interindividual variation in the phase-I metabolising enzymes of the cytochrome P450 (CYP) system is a widely recognized source of between-patient differences regarding drug therapy response,[9] and plays an important role in drug safety. Here, we want to focus on two enzymes involved in phase-I drug metabolism as markers of pharmacological variability, namely the CYP3A and CYP2D6 subsystems of CYP. The CYP2D6 and CYP3A enzymes together are responsible for about 60–75% of phase-I reactions undergone by all drugs metabolised through the CYP system and show extensive interindividual variation.[9] Also, these enzymes play an important role in many drug interactions.

The pathway from being a substrate of a metabolising enzyme system to complexities in clinical practice wit finding the 'right' dose, and as a possible consequence a change in a dose measure such as the DDD, is long and may be full of erratic features (e.g. publication of new clinical trial results, marketing by the industry and changes in good practice guidelines). However, although the DDD is not an average recommended dose by definition, a DDD change can be seen as a reflection of 'noise' surrounding the dosing of drugs in daily practice, indicating situations where the actual prescribed dose has departed significantly from the labelled use at the moment of setting the DDD. Accordingly, we use the DDD as a measure for problematic dose setting in this study.

We hypothesise that drugs metabolised through these variable enzyme systems are more susceptible to changes in dosage after marketing authorisation and, consequently, the need for a DDD change. Therefore, the main aim of our study was to determine whether substrate drugs for CYP2D6 and/or CYP3A enzymes are more prone to post-marketing DDD adjustments.

From a drug safety perspective, special interest goes out to post-marketing DDD decreases, since these represent cases where the average prescribed dose was lowered over time, possibly instigated by safety concerns or the 'overdosing' of the drug after introduction.

METHODS

We used a design comparable to that used in the previously mentioned study on DDD changes.[4] Again, we made use of a case-control design for the analysis. Cases were drugs with a DDD change between 1982 and May 2004. Only the first DDD change of a drug was included. Controls were randomly selected from all other drugs for which a DDD was available. Excluded from the analysis were drugs with a topical action, laxatives, drugs acting on the respiratory tract and stomatological preparations, since these drugs probably have a limited systemic absorption. Products with multiple active ingredients and drugs that show a high between-patient dose variability due to a strong relationship between dose and disease state (e.g. insulin, anti-anaemic preparations) were also excluded. Furthermore, we excluded drugs with a low volume of use in Europe; only

drugs that were marketed in the Netherlands were included in the analysis. For each case, two controls were randomly selected.

Information about the DDD changes, drugs and route of administration was retrieved from the website of WHOCC-DSM.[10] Year of global introduction of a drug was ascertained, since this was a determinant in the previous study.[4] Information on whether drugs were substrates of the CYP2D6/CYP3A enzymes was retrieved from the so-called 'Flockhart' CYP drug-interaction table.[11]

To adjust for possible bias introduced by the prominence of a drug in the scientific literature, we calculated a measure of 'attention exposure' in medical journals. For all cases and controls, the sum of citations in MEDLINE as a fraction of the total number of MEDLINE citations in 2 years before an index year was ascertained.

All results were calculated using a logistic regression model and presented as odds ratios (ORs) with 95% confidence intervals (95%CIs). In the model, metabolism pathway, route of administration and decade of registration were entered as categorical variables, 'attention exposure' in medical journals as a continuous variable.

RESULTS

We included 88 cases and 176 controls. Of the 88 cases, 51 were dosage decreases (58.0%). An overview of the cases and controls is displayed in Table 1.

The distribution of the fraction of MEDLINE publications (not shown in table) indicated that drugs with reported DDD changes were more widely covered than controls in the medical literature (p=0.036).

Being a substrate for either the CYP2D6 or CYP3A4 metabolism pathway was not significantly associated with any DDD change (OR 1.92; 95%CI 0.78–4.72). However, when we looked at only dosage decreases, the unadjusted OR for metabolism through CYP2D6 or CYP3A (9 of 51 cases versus 11 of 176 controls) was 3.21 with a 95%CI from 1.25 to 8.26. Table 2 shows the unadjusted and adjusted ORs for DDD decreases.

When CYP2D6/CYP3A metabolism results were entered into the regression model together with the influence of the administration route, the effect of the metabolic pathway on DDD decreases remained basically the same (OR 3.97;

95%CI 1.35–11.67). Adjustment for the number of publications on a specific compound had no large effect (OR 3.03; 95%CI 1.17–7.87). CYP2D6/CYP3A metabolism and decade of registration were also included in the logistic model, since early registration may be associated with less information about the metabolic pathway, fewer changes in dosing due to more experience with the drug, and not having had a post-DDD-setting review by the WHO during the study period. In this variant, the effect of CYP2D6/CYP3A on dosage decreases lost significance (OR 2.78; 95%CI 0.98–7.90).

TABLE 1 – Characteristics of cases of Defined Daily Doses changes (all) and controls

	CASES n=88 (100%)	CONTROLS n=176 (100%)	CRUDE OR OR (95%CI)
Period of introduction			
≤ 1970	24 (27.3%)	105 (59.7%)	Reference
1971 – 1980	22 (25.0%)	24 (13.6%)	4.01 (1.94 – 8.31)
1981 – 1990	25 (28.4%)	25 (14.2%)	4.38 (2.15 – 8.90)
≥ 1991	17 (19.3%)	22 (12.5%)	3.38 (1.56 – 7.32)
Administration route			
oral	59 (67.0%)	106 (60.2%)	Reference
non-oral/multiple	29 (33.0%)	72 (39.8%)	1.34 (0.79 – 2.30)
Metabolised by:			
CYP2D6 or/and CYP3A	10 (11.4%)	11 (6.4%)	1.92 (0.78 – 4.72)
CYP3A4	6 (6.8%)	7 (4.0%)	1.77 (0.58 – 5.42)
CYP2D6	5 (5.7%)	4 (2.3%)	2.59 (0.68 – 9.90)
CYP3A4 and CYP2D6	1 (1.1%)	0 (0.0%)	NA

OR = Odds Ratio; NA = not applicable

TABLE 2 – Odds Ratios (OR) for Defined Daily Doses decreases in drugs metabolised by CYP2D6 or CYP3A4

	OR (95%CI)
Unadjusted	3.21 (1.25 – 8.26)
Adjusted for: – route of administration	3.97 (1.35 – 11.67)
– exposure in medical journals	3.03 (1.17 – 7.87)
– period of introduction	2.78 (0.98 – 7.90)

DISCUSSION

Optimisation of drug dosing is key to successful drug development.[5,8] We found that being a substrate for either CYP2D6 or CYP3A (i.e. combining the numbers for both groups) makes a drug about three times more prone to require its DDD to be decreased after market authorisation has been granted. Although this effect is diminished when adjusting for decade of introduction, a direction of effect remains. This implicates that patients with early prescriptions of these drugs immediately after introduction into clinical practice may be exposed to inappropriate dose regimens.

Phase-I metabolism is a process susceptible to a great amount of variance. Differences in metabolising activity and henceforth larger variability in plasma levels and half-life can result in a greater variation in patient responses. The nature of the variability is different for CYP2D6 and CYP3A metabolism: for CYP2D6 it is caused by different alleles, resulting in a multi-modal distribution of enzyme activity; the origin of variability in CYP3A metabolism is still the subject of discussion, but a multi-gene or gene-environment interaction is suggested by the unimodal nature of enzyme activity.[12] In this study, we have tried to link these intrinsic drug properties, while disparate in character, to outcomes that are relevant from both clinical and regulatory perspectives.

Of course, there are many other sources of variability besides CYP3A and CYP2D6 that influence dosing of drugs and that need to be explored further in the future. For example, variability in other metabolising pathways, in absorption, in distribution or in drug targets.

Recently, Kircheiner et al.[13] reviewed the influence of phenotype on drug response for antidepressants and antipsychotics and pointed to the complex nature and consequences that multigenic and gene-environment interactions at different stages may have on treatment recommendations; response to antihypertensive agents is also known to be dependent on phenotype.[14]

For certain, there are other non-drug factors that are also of influence. In this study, the decade of registration was a strong predictor for undergoing a DDD change; this was also found in our previous study.[4] The reason for this could be that, because of the extensive experience with drugs marketed before 1970, good dosing strategies had already been developed in clinical practice long before the DDD methodology was introduced in the mid-1970s.

Although we consider the methodology employed here useful to gain insight into the studied process, there are some limitations that have to be addressed. First of all, the DDD changes included in this study possibly represent an underestimation of changes from the initial prescribed dose in daily practice. To minimize effects on drug utilisation studies, the number of DDD changes is kept as low as possible. Often only changes in the average maintenance dose of 50% or more warrant a DDD change. For recently established DDDs and major drugs, an exception is made; here smaller DDD adjustments are possible. Also, some changes might be made for pragmatic reasons.[10]

Bias may also have been introduced by the fact that well-known drugs are more likely to undergo a change in the DDD and also have their metabolism pathway elucidated. We tried to adjust for this by introducing the fraction of MEDLINE publications as a parameter, including the influence of the decade of registration and excluding drugs not often used in Europe. Furthermore, the table used for determining enzyme substrates of drugs does not indicate the primary metabolic pathway and may not be complete. However, the table is widely used as a reference guide and provides the evidence base for the reported metabolic pathways by referring to relevant publications.

One may argue that every need for adjustment of the dose after marketing is a failure of drug development and/or the regulatory system.[4] For sure, predictability of pre-marketing research with respect to patient outcomes after drug approval has improved significantly during the last decades. This paper warrants an ongoing strive to invest in the linking of in vitro data on, for example, metabolising properties of drugs with evaluations in real clinical practice.[15]

CONCLUSION

In conclusion, our study indicates that CYP2D6 or CYP3A substrates are more likely to require a DDD decrease after granting of market authorisation. However, this effect was diminished by adjusting for period of introduction. The implication of this finding is that variability indicators, as is demonstrated in this study for CYP2D6/CYP3A metabolism, can exert their influence on a wide variety of drug measures, such as the DDD.

For the future, the interactions between variability in dosing and variability indicators, whether pharmacodynamic or pharmacokinetic, warrant further investigation.

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chapter 2.2

chapter 2.2

Variability in use of newly approved drugs with or without an orphan designation

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ABSTRACT

Introduction

Regulators and third party payers have to strike a balance between the needs of the individual patient and the optimal allocation of scarce resources. Orphan drugs, are a special group of in this context because of high per unit costs and for usually not being able to fulfil the standard cost-effectiveness criteria. Our objective is to determine how utilisation of centrally authorised drugs varies across a selection of EU (European Union) member states, and in particular to determine whether drugs that have received an orphan drug designation show a different level of variability in use than drugs without an orphan drug designation.

Methods

We selected five orphan drugs and nine other centralised drugs that were centrally authorised in the EU between 1 January 2000 and 30 November 2006 and could also be used in the ambulatory setting. We compared utilisation of these drugs in seven EU member states: Austria, Denmark, United Kingdom (represented by England), Finland, Portugal, The Netherlands, and Sweden. Utilisation data was expressed as Defined Daily Doses (DDDs) per 1000 persons per year. For each drug relative standard deviations (RSD) across countries were computed as a measure of variability in use. Per treatment costs and innovativeness for each drugs were determined.

Results

Drugs with an orphan drug designation are, in general, more expensive and have a higher innovation score than drugs without an orphan drug designation. We found no association between orphan drug designation status and variability in use across countries.

Conclusion

Orphan drugs show no larger variability in utilisation than drugs without an orphan drug designation. Heterogeneity in use may be a feature of the drug market in the EU in general, and not restricted to one class of drugs.

INTRODUCTION

In every health system regulators and third party payers have to strike a balance between the needs of the individual patient and the optimal allocation of scarce resources. For new pharmaceuticals, national regulations and traditions are important determinants for how individual drugs are embedded in the system. Therefore, studying the variation in uptake of drugs across health systems can provide information on how access to new therapies differs from one country to another. Drugs indicated for the treatment or rare diseases, so called orphan drugs, are a group of special interest in this context because of their high per unit costs and for usually not being able to fulfil the standard cost-effectiveness criteria, that are often used in reimbursement decisions.[1] As a result, organisations such as the European Organisation for Rare Diseases (Eurordis), have called attention to the heterogeneous and incomplete availability of Orphan Drugs in the European Union (EU).[2]

At the EU level, the European Medicines Agency (EMEA) provides a centralised marketing authorisation procedure for new medicinal products, with a harmonised Summary of Product Characteristics (SmPC), for the whole EU since 1995. Therefore, the EMEA centralised procedure allows the comparison of the response of different EU health systems for drugs of which the quality, safety and efficacy was assessed by one and the same institution.

Currently, the centralised procedure is mandatory for biotechnology drugs and for all medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases. The procedure is mandatory for Orphan Drugs (ODs) as well. A centralised procedure is optional for medicinal products constituting a therapeutic, scientific or technical innovation (e.g. new chemical entities).

Our objective in this study is to determine how utilisation of centrally authorised drugs varies across a selection of EU member states, and in particular to determine whether drugs that have received an orphan drug designation, and therefore may be more vulnerable to heterogeneity in access and use, show a different level of variability in use than centrally authorised medicines without an orphan drug designation.

METHODS

Study population

We selected fifteen drugs that were centrally authorised in the EU between 1 January 2000 and 30 November 2006 and could also be used in the ambulatory setting. We randomly selected five ODs: imatinib mesilate (Glivec®), bosentan (Tracleer®), zinc acetate dihydrate (Wilzin®), nitisinon (Orfadin®) and sodium oxybate (Xyrem®). In addition, we randomly selected ten other/non-orphan drugs: levetiracetam (Keppra®), desloratidine (Aerius®), telmisartan/hydrochlorothiazide (Kinzalkomb®), emtricitabine (Emtriva®), apomorfine (Uprima®), adefovir dipivoxil (Hepsera®), oxybutinin (Kentera®), pregabalin (Lyrica®), efalizumab (Raptiva®), abacavir/lamuvidine (Kivexa®).

In our initial selection we also included apomorfine (Uprima®), but since the market authorisation was not renewed for this drug in 2006, and because the drug was only marketed in a few of the countries in this study, we excluded it from our final analysis.

We retrieved information about the utilisation of these drugs in seven European Union member states countries: Austria, Denmark, United Kingdom (represented by England), Finland, Portugal, The Netherlands, and Sweden. These countries represent a selection of EU member states from different regions and with different health systems.

Utilisation rates of drugs included in the study

Utilisation data was requested for all countries included in the study. We calculated drug utilisation rates used as a measure of uptake in the health system. We determined utilisation rates for the year 2006, as this was the latest full calendar year in the study period.

Utilisation rates were expressed as the number of Defined Daily Doses (DDD) per 1000 inhabitants per year. The DDD is a standard dosage measure defined by the World Health Organisation.[3] If DDDs were not available for a drug we defined the DDD ourselves based on information about the average daily dose contained in the official drug label.

Variability

Between country variability was determined by calculating relative standard deviation (RSD) for the utilisation rates of individual drugs across countries. This measure for variability was calculated as follows:

$$100 \times \frac{\text{Standard deviation of class utilisation as \% of total antihypertensive use}}{\text{International average of class utilisation as \% of total antihypertensive use}}$$

This method for calculating the variability in utilisation was used elsewhere as well.[4] Utilisation rates equal to zero were excluded from further analysis.

Innovativeness

Innovativeness of individual drugs was rated according to a system based on an algorithm designed by Motola et al.[5] This algorithm divides newly marketed drug in five classes according to two dimensions of therapeutic innovation; availability of other treatments and the therapeutic effect. Scores for availability of other treatments ranged from 5: drugs for diseases without recognised standard treatment to 1: mere technological innovation. Scores for therapeutic effect ranged from 3: major benefit on clinical endpoints or validated surrogate endpoints to 1: minor or temporary benefit on some aspects of the disease. All drugs included in the study were ranked according to the two dimensions of innovation in this system. Where available, we used a list compiled Motola et al. which was available from their website.[6] For drugs for which no score was available, the innovativeness was rated by two of the authors (HH and PS). We calculated the product of both scores as numeric indicator of therapeutic innovativeness for all products in the study.

Cost

As an indicator for cost differences between drugs we sampled the prices for each drug in three of the countries in this study (Denmark, The Netherlands and Sweden). Within each country, we ranked all drugs according to their price per DDD. Based on the average within-country price ranking of in each of the countries we determined an overall price rank for each drug. A score of 1 was assigned to the cheapest drug; a score of 14 was assigned to the most expensive drug.

RESULTS

The basic characteristics of the seven countries included in this study are shown in Table 1. This Table also provides information about the data sources from which the utilisation data in this study was retrieved.

TABLE 1 – Characteristics of countries (Source: OECD Health Data 2007 and EuroStat; all data for 2006)

	AUSTRIA	ENGLAND	FINLAND	NETHERLANDS	SWEDEN	DENMARK	PORTUGAL
Population (millions)	8.27	50.76	5.26	16.33	9.05	5.43	10.57
Population aged 65 and over (%)	16.3	16.0 [a]	15.9	13.8	17.3	15.1	17.0
GDP per capita (US Dollar)	34 394	32 896 [a]	30 911	35 112	32 111	34 110	20 030
Health expenditure as a share of GDP (%)	10.2	8.3 [a]	7.5	9.2	9.1	9.1	10.2
Pharmaceutical spending per capita (US Dollar PPP)	409	— [b]	380	318	351	276	445
Pharmaceutical spending (% of GDP)	1.2	— [b]	1.2	1.0	1.1	0.8	2.2
Automatic reimbursement for all marketed products [9]	No	Yes	No	No	No	No	No
Pharmacoeconomic assessment required for reimbursement [9]	Possibly	Pharmaco-economic evaluation may serve as guidance on whether a product should be used	Yes	Only for innovative medicines	Cost-effectiveness is one of the criteria which determines eleigibility for reimbursement	Not mandatory, sometimes a health economic analysis is used to justify a higher price	Only for innovative medicines

(Table 1 continued)	AUSTRIA	ENGLAND	FINLAND	NETHERLANDS	SWEDEN	DENMARK	PORTUGAL
Utilisation data source	Claims data of the Austrian sickness fund (PEGASUS-SV)	Electronic primary care prescribing information, collected specifically for reimbursement of drug costs	Ambulatory and hospital from the Finish National Agency for Medicines (www.nam.fi)	Ambulatory data from the GIP database (www.gipdatabank.nl)	Ambulatory data from www.apoteket.se	Ambulatory and hospital data from the Danish Medicines Agency (www.medstat.dk)	Information Drug Consumption System (SICMED); dispensing data of ambulatory care nationwide and IMS for hospital data
Data type	Reimburse-ment	Reimbursement	Dispensing	Reimbursement	Dispensing	Dispensing	Dispensing

GDP = Gross Domestic Product; PPP = Purchasing Power Parity
a) Data for whole United Kingdom.
b) Indicates that data was not available from OECD.

TABLE 2 – Overview of the drugs included in the study

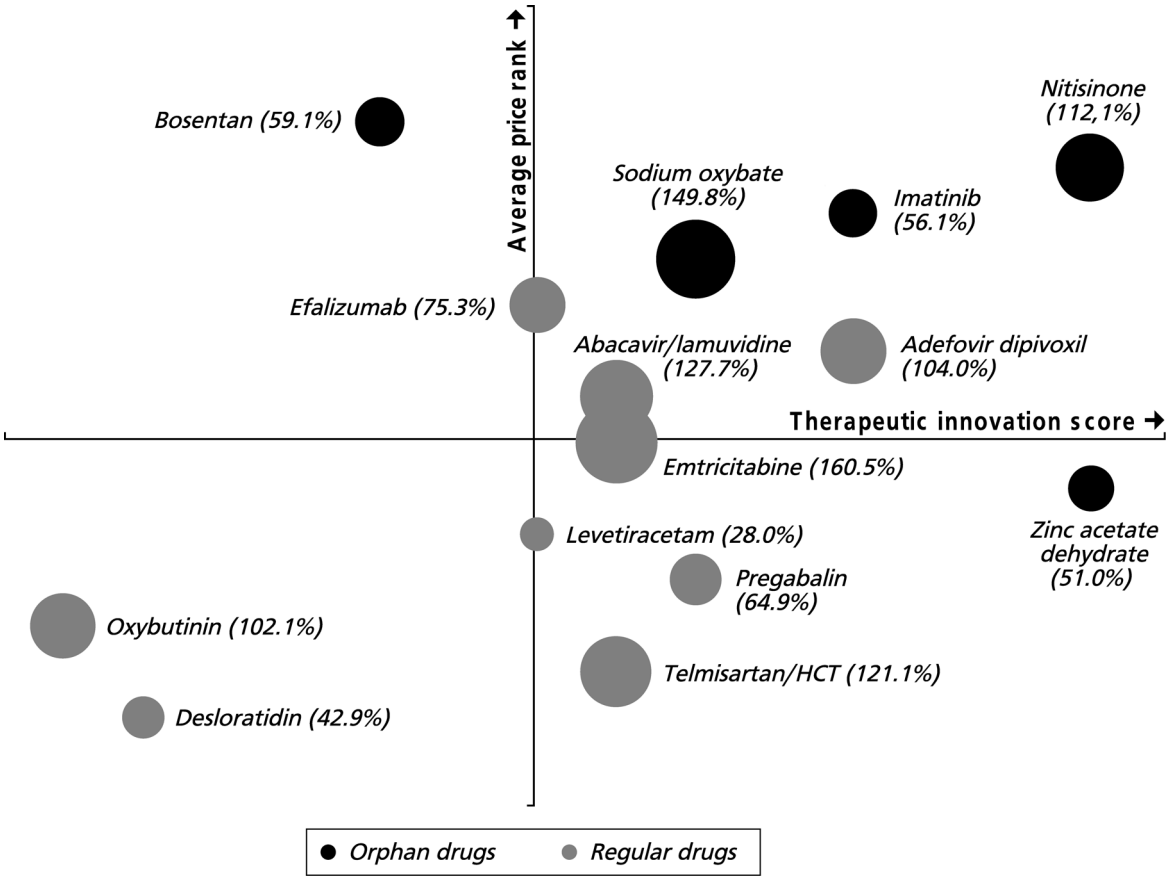
ACTIVE SUBSTANCE	MARKET AUTHORISATION DATE	INDICATION	DDD	INNOVATION SCORE	PRICE RANKING	RSD FOR UTILISATION	NUMBER OF COUNTRIES WITH >0 UTILISATION
With orphan designation							
imatinib	11 Nov 2001	Chronic myeloid leukaemia, acute lymphoblastic leukaemia, myelodysplastic/myeloprolifera-tive diseases, advanced hypereosinophilic syndrome (HES), chronic eosinophilic leukaemia (CEL), metastatic malignant gastrointestinal stromal tumours, dermatofibrosarcoma protuberans	400 mg [a]	12	12	56.1%	6
bosentan	15 May 2002	Pulmonary arterial hypertension	0.25 g	6	14	59.1%	7
zinc acetate dehydrate	13 Oct 2004	Wilson's disease	0.15 g	15 [b]	6	51.0%	6
nitisinone	21 Feb 2005	Hereditary tyrosinemia type 1	20 mg	15 [b]	13	112.1%	5
sodium oxybate	13 Oct 2005	Cataplexy in adult patients with narcolepsy	7.5 g	10 [b]	11	149.8%	4
Without orphan designation							
levetiracetam	29 Sep 2000	Epilepsy	1.5 g	8	5	28.0%	7
telmisartan/HCT	19 Apr 2002	Essential hypertension	65 mg [c]	9 [b]	2	121.1%	5

ACTIVE SUBSTANCE (Table 2 continued)	MARKET	INDICATION	DDD	INNOVATION SCORE	PRICE RANKING	RSD FOR UTILISATION	NUMBER OF COUNTRIES WITH >0 UTILISATION
emtricitabine	24 Oct 2003	HIV-1 infected adults and children in combination with other antiretroviral agents	0.2 g	9 [b]	7	160.5%	6
adefovir dipivoxil	6 Mar 2003	Chronic Hepatitis B	10 mg	12	9	104.0%	6
oxybutinin	26 Feb 2004	Treatment of the symptoms of urge incontinence and/or increased urinary frequency	15 mg	2	3	102.1%	7
pregabalin	6 Jul 2004	Treatment of peripheral and central neuropathic pain	0.3 g	10 [b]	4	64.9%	7
efalizumab	20 Sep 2004	Treatment of moderate to severe chronic plaque psoriasis	10 mg	8 [b]	10	75.3%	6
abacavir/lamuvidine	17 Dec 2004	Combination therapy for the treatment of HIV infection	0.9 g [c]	9 [b]	8	127.7%	7
desloratidine	21 Sep 2000	The relief of symptoms associated with: allergic rhinitis and chronic idiopathic urticaria	5 mg	3	1	42.9%	7

DDD = defined daily doses; RSD = relative standard deviations; HCT = hydrochlorothiazide; HIV = Human Immunodeficiency Virus
a) DDD determined by authors based on literature, not WHO-CC (World Health Organisation Collaborating Centre for Drug Statistics Methodology).
b) Innovativeness score determined by authors based on algorithm by Motola et al.[5]
c) Combination preparation, DDD determined according to WHO guidelines.

Table 2 provides an overview of the fourteen drugs included in the final analysis. For each drug, the date of EU market authorisation, the indication, the DDD used in the analysis, the innovation score, the price ranking, and the RSD for the utilisation rate across the seven countries are reported. As the Table shows, drugs with an orphan drug designation are, in general, more expensive and have a higher innovation score than drugs without an orphan drug designation.

FIGURE 1 - Variability in use of drugs in 2006 in an innovativeness vs. price matrix



Horizontal axis describes therapeutic innovativeness, while vertical axis describes average price rank. The size of the bubbles describes the variation in utilisation across the countries in the study. No statistically significant difference in variation in utilisation can be observed (p=0.80).

In Figure 1 we have displayed the relationship between, cost, innovativeness and variability in utilisation for each of the drugs. The innovativeness score for each drug is depicted on the x-axis, the y-axis shows the cost ranking, while the bubble sizes denotes variability in utilisation. The dark gray bubbles are orphan

drugs, the light gray bubbles are drugs without an orphan drug designation. The Figure can be divided in roughly four quadrants. The lower left quadrant contains drugs with a low score for innovativeness and low treatment costs. The upper right quadrant contains drugs with a high innovativeness score and high treatment costs. An independent samples t-test showed that there is no association between variability in utilisation and orphan drug designation status (p=0.80).

DISCUSSION

The results from this study show that the variability in use for Orphan Drugs appears to be comparable to the other newly authorised drugs that were included in the analysis. This means that, although strong heterogeneity in access may exist, orphan drugs may not be a 'special' group in this respect; heterogeneity may be an intrinsic aspect of the drug market in the European Union as a whole.
Orphan Drugs rated higher on an innovativeness rating system than the drugs without an Orphan Drug designation. This is not surprising, since the requirements for an orphan designation are strongly congruent with the requirements for an 'Important' innovation in the model of Motola et al.[5] One of the requirements for a drug to be eligible for an orphan drug designation is that "there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition."[7]
Given the small sample sizes, it is very difficult to disentangle the specific contributions of innovativeness and cost to the variability in utilisation. However, this study gives an indication that neither cost, nor innovativeness or an orphan status influences the variation in utilisation between the countries in the study. Therefore, this study indicates that access to orphan drugs should be viewed in a broader context of access to medicines in general. Furthermore, access should not be measured as a binary variable. Whenever studying access to certain drugs, especially when comparing multiple health systems that are characterised by diverging rules and regulations, access should be considered in the light of actual use in clinical practice.

Certain limitations apply to this study. When including per unit treatment costs in our analysis we used a method of ranking drugs according to their cost per DDD which only included costs in three countries, disregarding costs in the four other countries in the study. However, given the small variation in relative costs between these three European countries, it's unlikely that relative costs in the other four countries in the study would differ significantly. We have no reason to believe that the relative prices for the drugs in this study would show large variations when these other countries would have been included as well.

Furthermore, we only looked at the national level in this study and did not take regional variation into consideration. Access to, and use of, drugs may show large regional variability, for example, depending on policy and budget considerations of individual hospitals or insurance companies.[8]

Another limitation is that we did not include the prevalence of the diseases into our analysis. For some of the primary indications of drugs included in this study the prevalence may vary across countries, thus leading to an overestimation of the relative standard deviation measure for the utilisation of these drugs. Also, for zinc acetate, compounded alternatives may be available, which would make our measurement of the utilisation of this drug an underestimate.

The data sources used in this study consisted of reimbursement and dispensing data. Therefore, our results may have been influenced by differences between reimbursement and utilisation within countries or by differences by the method of procurement (public pharmacy, hospital pharmacy or both). As this limitation is an inherent characteristic of the data, we have indicated the source of all our data in Table 2. It also indicates that there is a need for a harmonised method of data collection on drug utilisation within Europe.

Finally, the countries included constitute a selection of EU member states. Results from this study should be extrapolated to other EU member states with caution, in particular for those countries that joined the EU on or after 1 May 2004. These countries may well have specific challenges with access and use of newly authorised drugs.

In conclusion, we found that orphan drugs show no larger variability in utilisation than drugs without an orphan drug designation. Therefore, heterogeneity in use may be a feature of the drug market in the EU in general, and not restricted to one class of drugs. We would like to argue for studies on access issues to take this variability in use into account. Future studies looking at

access issues should also take into account the actual utilisation for a comprehensive assessment of this topic.

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chapter 2.3

Rare essentials: drugs for rare diseases as essential medicines

This chapter is based on an invited discussion paper for the 14th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines (7-11 March 2005, Geneva, Switzerland)

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ABSTRACT

Since 1977, the World Health Organisation (WHO) Model List of Essential Medicines (EML), has provided advice for Member States that struggle to decide which pharmaceutical technologies should be provided to patients within their public health systems. Originating from outside WHO, an incentive system has been put in place by various governments for the development of medicines for rare diseases ('orphan drugs'). With progress in pharmaceutical research (e.g., drugs targeted for narrower indications), these medicines will feature more often on future public health agendas. However, when current definitions for selecting essential medicines are applied strictly, orphan drugs cannot be part of the WHO Essential Medicines Programme, creating the risk that WHO may lose touch with this field. In our opinion WHO should explicitly include orphan drugs in its policy sphere by composing a complementary Orphan Medicines Model List as an addition to the EML. This complementary list of 'rare essentials' could aid policy-makers and patients in, for example, emerging countries to improve access to these drugs and stimulate relevant policies. Furthermore, inconsistencies in the current EML with regard to medicines for rare diseases can be resolved. In this paper we propose selection criteria for an Orphan Medicines Model List that could form a departure point for future work towards an extensive WHO Orphan Medicines Programme.

INTRODUCTION

In all health-care systems, there is a struggle to decide which technologies should be provided to patients within the system. Criteria such as efficacy, need, prevalence and cost-effectiveness are used in this selection process. These struggles are particularly acute when considering pharmaceuticals. Since 1977, World Health Organisation (WHO) has provided advice for countries by defining a WHO Model List of Essential Medicines (EML).[1] The concept of the EML as normative guidance and technical support has helped over 150 countries to establish the principle that essential medicines save lives and improve health, but only when they are available, affordable, of good quality, and properly used.[2] The fourteenth edition of the EML was published recently.[3] Originating from outside WHO, an 'orphan drugs' movement has developed primarily in affluent countries since the early 1980s to create incentives for the development of medicines for rare diseases.[4] Because of their small market potential, such drugs are not attractive for pharmaceutical companies to develop and market.

While both are systems of prioritising resources and allocating incentives for pharmacotherapy, the orphan drug movement and the WHO Essential Medicines Policy have many differences in background, goals and conceptual frame. However, it is becoming increasingly clear that they share common ground, i.e. there are essential medicines for rare diseases. Although orphan drugs have not been on the priority agenda of WHO because there are urgent population health needs with a high disease burden to be met, this may change as more orphan drugs come onto the market. For example, orphan drugs currently constitute about 15% of new centralised authorizations in the European Union (EU), there is increasing attention for 'rare diseases' in emerging countries (e.g. Egypt, India) and more spin-offs of orphan drug innovations with implications for drug treatment in general (e.g. imatinib mesylate, used for the treatment of chronic myeloid leukaemia).[5] In this paper, we review recent advances in the fields of orphan drugs and essential medicines, and propose how WHO may develop an approach to provide useful advice to Member States that want to improve access to treatments using orphan drugs. For this purpose, we would like to recommend the creation of a complementary WHO Model List for Orphan Medicines as an addition to the current EML. Furthermore, we aim to

provide a framework for analysing future questions surrounding the selection of 'essential orphan medicines' or 'rare essentials'.

MEDICINES FOR RARE DISEASES: SMALL NUMBERS WITH IMPACT

"Which diseases are classified as rare?" is not an easy question to answer, as we have to deal with a complex mosaic of hard-to-categorise conditions. Many rare diseases have a genetic basis. Often this is a monogenic modification, as in the case of X chromosome-linked haemophilia or the defect in transmembrane chloride ion transportation that causes cystic fibrosis.

Currently, several criteria to identify and classify rare diseases are found in orphan drug legislation, which provides incentives for the development and marketing of medicinal products for diseases that may otherwise suffer from non-viability of the market. These market failures are mainly caused by scientific deficiencies (e.g. small numbers of subjects for clinical trials, lack of knowledge about the cause of the disease, absence of valid biomarkers), greater regulatory demands on new drugs in terms of safety and effectiveness, possible obstacles in patenting, and a lack of public awareness of the issue.[6] In response to this, the first orphan drug legislation was introduced in the United States of America (USA) in 1983. Other countries (e.g. Australia, Japan, Singapore) followed in the 1990s, and in 2000 the EU established its own orphan drug legislation. Table 1 provides an overview of the main features of orphan drug systems in the EU and USA. Methods used in regulations to stimulate research and development of orphan drugs include extended regulatory guidance and advice, waivers of regulatory fees and market exclusivity. It is important to note that there are differences between the USA and EU definitions of a rare disease. In the USA Orphan Drug Act, the definition relates to an absolute number (<200 000 patients in the USA), while the European regulation uses a relative measure (<5 cases per 10 000 inhabitants) and requires disorders to be life-threatening and/or chronically debilitating. When these definitions are used, it is estimated that between 5000 and 7000 conditions qualify as rare diseases, bringing the total number of patients suffering from these diseases in Europe and the USA alone to 55 million.[4,7] For many other countries data are scarce, but the prevalence of rare diseases is likely to be comparable.

TABLE 1 – Features of the USA and EU Orphan Drug incentive system [11]

	USA	EU
Program established	1983 – Orphan Drug Act modified the Federal Food, Drug and Cosmetic Act	2000 – Orphan Medicinal Products Regulation
Prevalence criterion for rare disease	Less than 200 000 patients in USA (<7.5:10 000)	Life-threatening or chronically debilitating disorder that affects less than 5:10 000 in EU
Requirements for designation	Rare disease, or R&D costs cannot be recovered in 7 years	Rare disease, or product unlikely to be developed without incentives, or new product will be of significant benefit
Products eligible for orphan designation	Drugs and biologicals (including vaccines and in vivo diagnostics)	Drugs and biologicals (including vaccines and in vivo diagnostics)
Market exclusivity	7 years; prevents same product being approved for the same indication unless clinical superiority is shown	10 years; can be reduced to 6 if orphan criteria are no longer met
Other benefits	Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharma and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food	Regulatory fees can be reduced or waived; access to centralised procedure; protocol assistance. Individual Member States have to implement measures to stimulate the development of orphan medicinal products.

USA = United States of America; EU = European Union

To prioritise limited public health resources it is important to possess reliable data on disease burden, course of disease and long-term prognosis. This has been a difficult task for rare diseases. A primary reason why sound epidemiological data is often lacking is the absence of proper classification and coding for the disease and the absence of registration of the patients suffering from rare conditions. Although International Classification of Disease (ICD) codes are available for some of the better-known rare diseases, such as thalassaemia, cystic fibrosis and haemophilia, many orphan drugs are not included in medical registries and databases. Often these rare disorders are grouped under higher classification levels such as 'endocrine metabolic disorders'. A second reason for the lack of reliable epidemiological data is the frequent absence of appropriate biochemical and genetic diagnostic data. Generally speaking, indicators to quantify disease burden,

such as the disability-adjusted life year (DALY), are not very useful in the case of rare diseases, as the low prevalence brings DALY estimates for these diseases to the bottom of any list created on the basis of burden of disease.

The impact of the Orphan Drug Act on drug development and public health in the USA was evaluated in 2003, the 20th anniversary of its establishment.[4] Since the introduction of this legislation, about 1100 drugs have received an orphan drug designation. Of these, 231 were marketed, providing an estimated 11 million patients in the USA with a new treatment for their disease. In the EU, the first 5 years of orphan drug legislation were recently evaluated by the European Medicines Agency (EMEA). Overall, the experience was positive; by April 2005, more than 260 products had acquired an orphan drug designation, and 22 of these received a marketing authorisation, creating new treatment options for more than one million patients in the EU.[8]

ACCESS TO AND AFFORDABILITY OF MEDICINES FOR RARE DISEASES

Despite this progress, no effective and safe treatment is available for many rare diseases. Furthermore, when treatments are available, obstacles are encountered that hinder access and use of these drugs.

- *Challenges in assessing clinical relevance and cost-effectiveness*. The methodology for evaluating orphan drug treatments is often still in an experimental phase, hampering positioning in clinical practice.
- *Lack of knowledge and training*. For many rare diseases, available information is inadequate. Health professionals are often deficient in appropriate training and awareness to be able to diagnose and adequately treat these diseases. The aim of initiatives like Orphanet[7] is to address this issue.
- *Deficient diagnostic systems*. For many diseases no diagnostic methods exist, or diagnostic facilities are unavailable. In these cases, diagnosis may be problematic. Consequently, validity, coding and reproducibility are problems.
- *High prices*. Prices of orphan drugs per treatment episode can be very high. For example, the cost of treatment with enzyme replacement therapies may reach more than US$ 150 000 per treatment-year. The affordability of orphan drugs has become a major issue for payers and is a strong driver of tensions

between the different stakeholders.[9] Some companies have responded to this by developing programmes to facilitate access to orphan drugs.[10]

These obstacles to treating rare diseases with orphan drugs exemplify and mirror the global debate of deficiencies in bringing new drugs to patients who need them. The recent WHO report Priority medicines for Europe and the World gives a thoughtful account of this and has provided a priority listing of gaps in pharmacotherapy.[11] One of these gaps is the crisis in the development of new antibiotics. This crisis was linked to the orphan drug issue in a more general context in Science magazine: "Will all drugs become orphans in the future, not because of the rareness of the disease, but because other factors hinder investment in drug discovery and development?"[12]

Furthermore, advances in pharmacogenomics may lead to treatments benefiting a small subgroup of patients.[13] Whatever the outcome, it seems inevitable that with an increasing number of drugs specifically indicated, and effective, for rare diseases, these medicines will feature more often on future public health agendas.

ESSENTIAL MEDICINES: BIG NUMBERS WITH IMPACT

In 1977, the first Essential Drug List was published, containing medicines that were indispensable for the health needs of the majority of the population.[1] By 2002, the definitions of the EML had changed. From then on essential medicines were selected with 'priority conditions' in mind: they had to be evidence-based, safe and cost-effective. Priority conditions were selected considering current and future public health relevance.[14] The EML consists of two sections, which are published together: a 'core' list representing the minimum medicine needs for a basic health-care system, and a 'complementary' list for medicines that address priority health-care needs, but require specialised facilities/services, or are costly. Within the context of the EML, medicines for 'neglected diseases' may be included in the list on the basis of the criteria described above since they meet the priority needs of a specific population (e.g. local high-prevalence conditions such as trypanosomiasis), in contrast to 'rare diseases' (diseases with a low prevalence everywhere).

Three major functions for the EML (and other WHO medicines policies) have been identified: operational, educational and symbolic purposes.[15] As an

operational tool, the EML is an important guide for policy-makers and programme managers to identify medicines that require priority attention in terms of production, and access. Furthermore, the list is an educational tool for health professionals and policy-makers, not only through improvement of formulary building and utilisation, but also through the procedures used to select WHO committee members and candidate medicines for the EML. Finally, the list has a significant symbolic value. Classification as an essential medicine confers worldwide recognition, preferred position in pharmaceutical management and may stimulate related policies (e.g. production, infrastructure investments or the establishment of quality systems).[16-18]

While selection occurs at a global level, the EML concept should be implemented nationally. Countries are invited and encouraged to formulate national policies with the EML as a model to be adapted. This results in separate national lists, which vary from the WHO list due to local circumstances such as demographics, epidemiology, public health relevance, financial resources or capacity of the health system. Whether a medicine is included in a national list can be considered as an indicator for the level of adoption and dissemination of the EML. A comprehensive overview of the differences between the EML and national lists can be found in an analysis published in the Lancet.[1] Although there is an ongoing debate about the impact of these lists on national drug use, the balance sheet for the EML, particularly in less affluent countries, looks very positive.[19]

ORPHAN DRUGS AND ESSENTIAL MEDICINES

Although the fields of essential medicines and orphan drugs share principles of social justice and equity, Table 2 lists some important ways in which the two groups of medicines differ.

Two recent examples illustrate the tensions in the discussion about orphan drugs within the WHO Expert Committee on the Selection and Use of Essential Medicines: the cases of fludrocortisone and factor VIII/IX concentrates. Fludrocortisone, indicated for adrenal insufficiency, was deleted from the EML in 2003, because its rare indication did not meet the criterion of "satisfying the priority health-care needs of the population", it was on few national lists, and

was not stocked by some major international suppliers.[20] In contrast, just 2 years later the 2005 Expert Committee decided to retain factor VIII and IX concentrates as essential medicines, even though haemophilia is a rare disease, like adrenal insufficiency.[21] Important arguments for keeping factor VIII/IX on the EML were the lack of safety and cost of the alternatives, and logistical arguments, such as the organisation required by blood transfusion services for the production of plasma fractions.

TABLE 2 – Essential Medicines and Orphan Drugs compared

	ESSENTIAL MEDICINES	ORPHAN DRUGS
Concrete policies in place since:	1977 worldwide	1983 in USA, 2000 in EU
Primary focus:	Public health – bringing effective medicines to as many patients as possible	Individual patient – even a single patient warrants everything that is possible
Initiated and developed by:	WHO, and member states	Governments of USA, Japan, Australia and EU; patient groups
Criteria:	Drug driven (e.g. drug to be listed at EML is efficacious, safe, cost-effective, based on evidence based data)	Disease driven (e.g. disease to be classified as OD has low prevalence <5–7.5: 10 000, is life threatening)
Policies directed at:	Bringing already available medicines to patients	Bringing new medicines to so far untreatable patients
Target populations:	Initially in less-affluent countries, now all countries	In affluent countries, developed world
Economics:	Cost-effectiveness, sustainable and affordable access	Relatively (very) high prices per individual patient, cost-maximisation per population

USA = United States of America; EU = European Union; WHO = World Health Organisation; EML = Essential Medicines List; OD = orphan drug

At the same meeting in 2005, the Committee suggested that there was a need for WHO to establish a policy advisory group on rare diseases to study this issue in light of its increasing importance.[21]

RARE ESSENTIALS

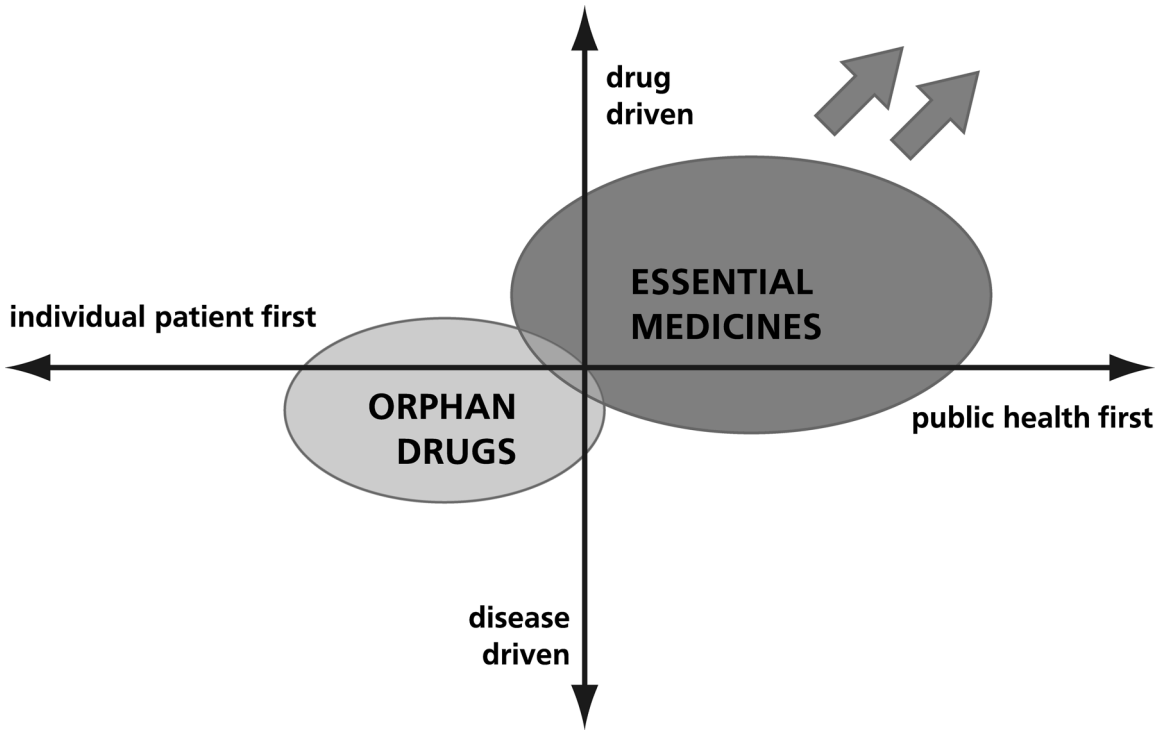
We started this paper with the notion that there is common ground between the EML and orphan drugs. However, developments in policies affecting the EML may result in these fields becoming more and more distinct in the future. The primary focus in the orphan drug arena is the individual patient, irrespective of the demands of society at large. This contrasts with the more 'utilitarian' public health approach of the current EML definitions. Moreover, the two systems also differ in their drug/disease orientation. Figure 1 captures these two dimensions. The domain of the EML is dominated by public health concerns (i.e., priority diseases) and proven effectiveness of medicines through the methods of 'evidence-based medicine'. The 2002 revisions of the EML entry criteria show an increased move towards the upper-right quadrant. Therefore, if current EML definitions are applied strictly, both fields may 'lose touch'. We believe that this is an unwanted situation given future developments in the pharmaceutical field. Below we propose criteria to compose a complementary Orphan Medicines Model List to assist policy-makers.

Priority-setting on medicines for rare diseases requires a thoughtful weighing of issues associated with disease prevalence, drug effectiveness, safety and costs. Although the driver of such a weighing process should be scientific evidence, it is important to note that for orphan drugs it is not always possible to meet state-of-the-art standards of evidence-based medicine, particularly when an orphan drug is newly developed and limited data are available on effectiveness, safety, tolerance, etc.[22] Therefore, we propose the following, primarily 'drug-driven', criteria for inclusion on a complementary WHO Orphan Medicines Model List, i.e. designation as a 'rare essential'.

1. *Prevalence*: the rare disease has a prevalence <5–7.5 cases per 10 000 persons (EU/USA criteria) and is life-threatening or chronically debilitating.
2. *No alternatives on EML*: no other medicine on the EML is an effective alternative treatment (the medicine may be on the EML for a different indication).
3. *Effectiveness*: the treatment is effective.
4. *Safety:* the treatment has a positive safety profile.
5. *Availability*: sustained supply of the product is feasible.

6. *Diagnosis*: the diagnosis of the disease is technically feasible (in most countries).
7. *Expertise infrastructure*: the specialist knowledge, training and infrastructure to diagnose and to treat the disease is available (in most countries).

FIGURE 1 - Two dimensions of bringing important drugs to patients



In this figure, 'drug driven' refers to more emphasis on the drug compound for decision-making (e.g. cost-effectiveness, evidence base); 'disease driven' refers to more emphasis on the characteristics of the disease in the decision-making process; the arrows indicate a future trend based on recent developments.

When a medicine does not fulfil the first criterion it should be evaluated according to the existing (2002) criteria for inclusion on the EML. The exact cut-off value for rare diseases used on the Orphan Medicines Model List can be the subject of future debate. When the disease prevalence is appropriate, criteria 2–7 should be evaluated. Especially for criteria 5–7, evaluation on a case-by-case basis is required. However, rules on how to weigh the evidence can be decided beforehand. If any of the criteria 2–7 cannot be met, the medicine would not be suitable to be included in a complementary Orphan Medicines Model List.

Using the criteria introduced above, we evaluated factor VIII concentrate as an example (Table 3). From this assessment it can be concluded that, although problems in diagnosing haemophilia and ensuring access to factor VIII concentrate remain, factor VIII fulfils all criteria and could be included on a complementary WHO Orphan Medicines Model List. The selection process proposed here is stringent. However, only a rigorously selected list can aid policy-makers in the target Member States.

TABLE 3 – The evaluation of Factor VIII concentrates according to the proposed criteria for an Essential Orphan Medicines List

CRITERIA	ASSESSMENT OF FACTOR VIII CONCENTRATE
1. *Prevalence*	In the USA about 18 000 people have haemophilia,[23] bringing the prevalence to less than 1 per 10 000 inhabitants. Prevalence in emerging countries is comparable.
2. *No alternatives on EML*	No alternative treatments are available on the EML.
3. *Effectiveness*	The treatment is regarded as highly effective for haemophilia A.
4. *Safety*	With a safe supply of blood products, Factor VIII is a safe product considering its indication.[24]
5. *Availability*	Programs like 'Operation Access' have improved the supply of this product in many countries.[25]
6. *Diagnosis*	Although laboratory infrastructure is often lacking,[26,27] good progress in diagnosis has been made; although this is still a problem in many countries. Several programmes have increased knowledge about the diagnosis and treatment of haemophilia A.[28]
7. *Expertise infrastructure*	Inclusion of blood products on the EML has been an important factor to facilitate and stimulate local infrastructure/training on blood transfusion.

EML = Essential Medicines List

OPTIONS

We propose three possible routes that WHO could take to address the issue of medicines for rare diseases:

- do not include medicines for rare diseases in WHO's policy sphere;

- create an Orphan Medicines Model List as a complement to the current EML;
- create a dedicated Essential Orphan Medicines Programme alongside the current Essential Medicines Department.

Doing nothing is not a viable option. With interest in rare diseases increasing, WHO should not exclude itself from this debate. Furthermore, the impact of granting a special status to the treatment for a specific rare disease can be illustrated by the case of haemophilia. Being listed on the EML has contributed to increased national investments in local safe blood transfusion infrastructure, education and training. If the WHO medicines policy does not give such symbolic attention to orphan drugs, these valuable opportunities may be missed, which would be a loss for all parties involved. These consequences and the need for action were also recognised by the WHO Expert Committee on the Selection and Use of Essential Medicines at its most recent meeting in March 2005.[21]

We want to argue for the second option presented above: creating an Orphan Medicines Model List as a complement to the current EML, using the experience and expertise available in the Essential Medicines Programme and Expert Committee. Furthermore, inconsistencies in the composition of the EML, as is the case with the current inclusion of factor VIII and IX concentrates, can be avoided. The selection criteria we have suggested above could aid in the process of selecting candidate drugs for an Orphan Medicines Model List. When this list appears to be successful, an extension to a more expensive independent WHO Orphan Medicines Programme can be considered.

CONCLUSION

We believe that WHO should explicitly include orphan drugs in its policy sphere as more orphan drugs will become available in the next decades and more Member States will face tough questions about how to address the need and demand for treatment by patients with a rare disease. High costs, the imbalance between industry and public health interests, problems with access and a lack of an evidence base are features that may hamper such an activity. However, considering orphan drugs solely as an issue for high-income countries does not

help policy-makers and patients in low-income countries to tackle the need for treatment. The establishment of an easily retrievable, international expert opinion on effective therapies for rare diseases would aid in formulating specific national policies aimed at improving access to orphan drugs. The EML has been an important symbolic, operational and educational tool for the past three decades. The same could be true of a complementary Orphan Medicines Model List that identifies 'rare essentials'.

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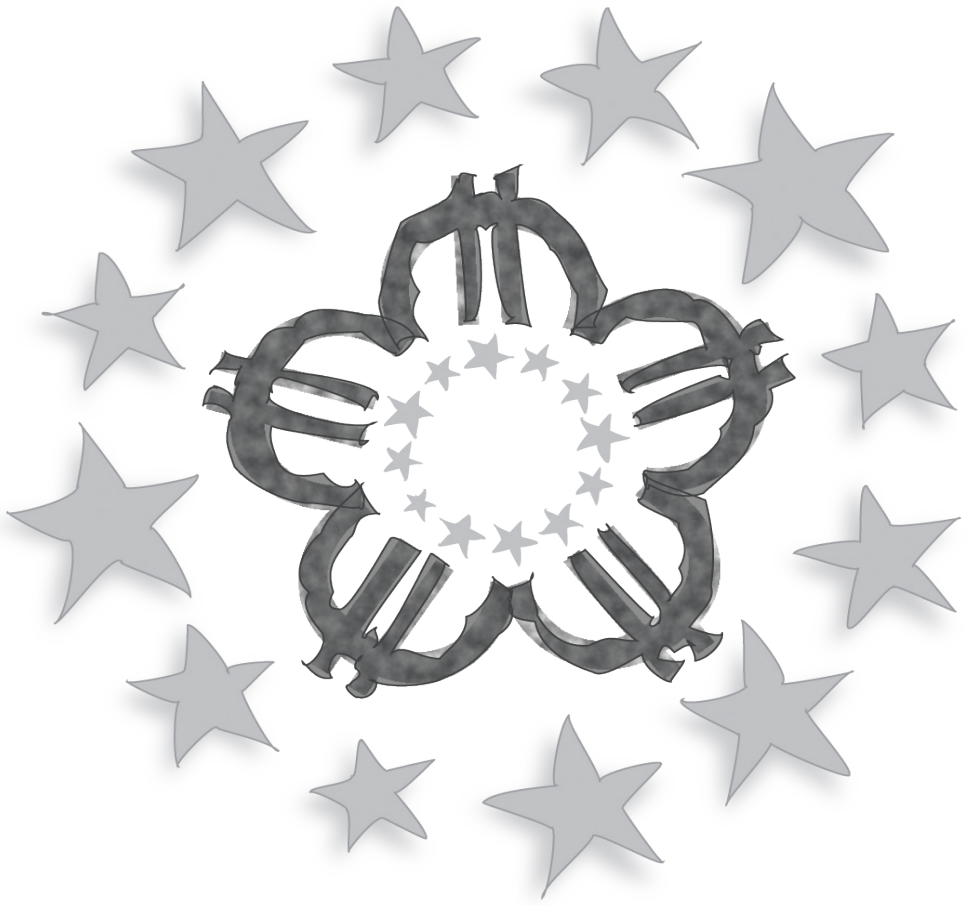
Effects of policy (interventions) on the use of drugs in clinical practice



chapter 3

chapter

chapter 3.1

chapter 3.1

Impact analysis of the discontinuation of reimbursement: the case of oral contraceptives

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ABSTRACT

Background

We studied the impact of suspending oral contraceptive (OC) reimbursement in the Netherlands for women >21 years starting 1 January 2004. Discontinuation and switching patterns and the time course of the policy intervention's effects were determined.

Methods

The intervention cohort contained OC users on 1 January 2004, the control cohort users on 1 January 2003. Follow-up duration was one year. Discontinuation and switching patterns were assessed using relative risks (RR). Weekly refill fractions were calculated to determine the time course of the policy effects.

Results

Our intervention cohort contained 434 917 OC users, the control cohort 489 904 users. When we excluded patients not affected by the policy intervention (i.e., all patients younger than 20 years). Discontinuation rates were 15.3% (intervention cohort) and 12.3% (control cohort) (RR 1.24; 95% confidence interval 1.23–1.26) and increased with age. Switching to cheaper OCs was greatest in the intervention cohort, particularly in the 40-44 years group. Differences in cumulative refill fractions showed large variation over time.

Conclusion

The OC reimbursement intervention led to a increase in the discontinuation rate of 24%. The effect increased with older age groups. Considering the time course of effects of policy interventions is of critical importance.

INTRODUCTION

In many European countries governments and third party payers strive to reconcile the policy goals of containing drug expenditures and stimulating the provision of good quality and accessible health care. For this purpose, various tools are used, including positive or negative reimbursement lists, cost sharing, price/profit controls, physician budgeting, formularies and guidelines.[1]

An important piece of evidence needed to make a decision about the allocation of resources in the pharmaceutical budget is the evaluation of the impact of policy measures on drug use in clinical practice. At the moment, these evaluations are scarce and are often not an integral part of the policy cycle. This was recently echoed in a Cochrane review that concluded that there are few well designed evaluations of pharmaceutical pricing policies and recommended that "because pricing policies have uncertain effects as well as benefits, it is important that they are properly evaluated".[2]

An analysis using prescription records could provide the information needed for such an evaluation of policy interventions related to pharmaceuticals. In this study, we want to explore the use of pharmacoepidemiological tools to study the impact of a reimbursement restriction for oral contraceptives (OCs), a drug class that is of particular interest because of its emblematic role in allowing women to make life-style choices as well as the wider social, political and ethical aspects involved.[3] On 1 January 2004 OCs were discontinued from the Dutch positive reimbursement list for women over 21 years of age.[4] The reason for this move was to contain short-term health care costs, aiming for a reduction in spending of 70 million euros. At the patient level, this led to an individual cost increase of about 50 euros per year.

Our primary objective in this study is to determine whether more women discontinued the use of OCs after 1 January 2004, the date of the reimbursement restriction, than in a historical control cohort that did not undergo the policy intervention. A secondary objective was to find out if more patients switched to cheaper OCs in the intervention cohort than in the historical control cohort. Finally, we assessed whether the timing of the impact assessment of the policy intervention could influence the results.

MATERIALS AND METHODS

Setting

During the study period, the Dutch health insurance system covered about two-thirds of the population (lowest incomes) by a mandatory sick fund system for most hospital and ambulatory health care claims, and the remaining third (highest incomes) by a voluntary and private system.

Pharmaceutical reimbursement in ambulatory care was based on a positive list of drugs that was formulated at the government level. A guiding principle for deciding whether a drug should be included on the reimbursement list was whether care was necessary, effective, efficient and could not be left to the individual's responsibility. In general, nearly the full price of a prescription drug on this list was reimbursed.[5] Up until 1 January 2004, OCs were part of the basic reimbursed package. After this date, and up until 1 January 2008, OCs were no longer reimbursed for women over 21 years of age. However, patients with supplementary health insurance did get a reimbursement for OCs in some cases.

Study cohort

Data were collected from the Dutch Foundation for Pharmaceutical Statistics (SFK) database. The database contains the dispensing histories of patients from 1 540 of 1 700 community pharmacies in the Netherlands.[6] In the database all pharmacies and all patients within a pharmacy have a unique identifier. For women aged between 15 and 44 years between 1 January 2002 to 31 December 2004, all prescriptions for oral contraceptives were selected, based on Anatomic Therapeutic and Chemical (ATC) classification system codes.[7]

We compared discontinuation and switching rates of OC use in a cohort undergoing the policy intervention (intervention cohort) to a historical control cohort (control cohort). The intervention cohort consisted of patients that were defined as users in 2003 and were followed-up for one year after the reimbursement restriction on 1 January 2004. The control cohort consisted of patients that fulfilled our definition of a user for 2002, and were followed for one year after 1 January 2003, a date without any policy interventions relating to OCs.

We excluded those pharmacies that had on average less than 100 prescriptions for an OC per month, or that did not report data for the full period of the study. We deemed the data from these pharmacies to be unreliable.

Definition of oral contraceptive use

Users were defined as patients who: 1) filled at least two prescriptions for an OC during a calendar year (2003 in the intervention cohort; 2002 in the control cohort); 2) had a supply of OCs on the index date. The index date was 1 January 2004 in the intervention cohort and 1 January 2003 in the control cohort. In the Netherlands, prescriptions for OCs generally have a duration of six months.

Discontinuation and switching

Discontinuation was defined as not filling a prescription for an OC after the index date for at least 365 days. Switching was defined as a change in the 'trade product code' when a new prescription was filled. Trade product codes are unique at level of the trade product name and dose. To determine whether patients switched to a cheaper or more expensive OC, we compared the pharmacy purchasing prices of the drugs, assuming that these price differences are also reflected in the final cost for the patient. When price differences were smaller than 5%, these were deemed too small to influence the decision process and were included in the 'same price' group. All results were stratified according to age and 'generation' of OC (first and second versus third generation).

Evaluation of time course

To determine the influence of the moment on which the impact of the policy intervention was evaluated, we calculated weekly refill fractions. The refill fraction is defined as the number of patients that returned in a given week to fill their prescription, divided by the total number of patients eligible for a refill (all patients in the cohort who have not yet filled a prescription after January 1st of the index year). The cumulative refill fractions and the differences between the cumulative refill fractions for the intervention and control cohort were depicted graphically. The applicability of this method has also been described elsewhere.[8]

Statistical analysis

To determine whether differences between the two cohorts were statistically significant with regard to discontinuation and switching, we calculated relative risks (RR) with 95% confidence intervals (95%CI).

RESULTS

Our intervention cohort consisted of 434 917 OC users, our historical control cohort contained 489 904 users. The basic characteristics of the patient population are shown in Table 1. After the index date, 60 549 users (13.9%) discontinued in the intervention cohort and 55 744 users discontinued in the control cohort (11.4%), the overall RR was 1.22 (95%CI 1.21-1.24). When we excluded the age group of which we were certain that it was not affected by the policy intervention (i.e. all patients younger than 20 years), the discontinuation rate was 15.3% in the intervention cohort and 12.3% in the control cohort (RR 1.24; 95%CI 1.23-1.26; see Table 2).

The discontinuation rates varied between the different age groups. In all age groups, except for patients younger than 20 years, who were unaffected by the policy, the RR was increased. The RR was highest in the 40-44 years age group (RR 1.45; 95%CI 1.39-1.50). When we stratified our analysis for the generation of OC that was used on the index date, we did not find meaningful differences between the various groups with regard to discontinuation of the OC.

The number of patients switching to another OC after the index date is shown in Table 3. As the table shows, there was an overall increase in switching to cheaper alternatives after the policy intervention. The RR for switching to cheaper OCs increased with age and was most pronounced in the 40-44 years age group (RR 1.28; 95%CI 1.14-1.43). In the age group unaffected by the policy intervention (<20 years) there was a decrease in the RR for switching; overall the RR was 0.90 (95%CI<0.85-0.96), for switching to cheaper OCs the RR was 0.91 (95%CI 0.83-0.99).

Cumulative refill fractions for each week after the index date are shown in Figure 1. The difference curve (dashed line) shows large variation in the difference of cumulative refill fractions over time between the intervention and control cohorts. Initially the cumulative refill fraction difference increased and reached a maximum after 21 weeks. After this, the difference curve declined towards the final overall discontinuation rate of 2.5%.

TABLE 1 – Characteristics of the patient population

PATIENT CHARACTERISTICS	POLICY INTERVENTION COHORT	POLICY CONTROL COHORT
Total number of women	434 917 (100%)	489 904 (100%)
Average age in years [SD]	28.91 [8.13]	28.94 [8.02]
Top 5 substance combinations used on index date:		
1- levonorgestrel and estrogen (fixed)	244 610 (56.2%)	258 239 (52.7%)
2- desogestrel and estrogen (fixed)	73 909 (17.0%)	92 566 (18.9%)
3- levonorgestrel and estrogen (sequential)	45 483 (10.5%)	55 180 (11.3%)
4- gestodene and estrogen (fixed)	36 828 (8.5%)	45 619 (9.3%)
5- lynestrenol and estrogen (fixed)	10 595 (2.4%)	12 554 (2.6%)
Generation of oral contraceptive on index date:		
1st or 2nd generation [a]	307 199 (70.6%)	333 519 (68.1%)
3rd generation [b]	116 586 (26.8%)	145 517 (29.7%)
other [c]	11 132 (2.6%)	10 868 (2.2%)

SD = standard deviation

a) Preparations containing: lynestrol and estrogen, norethisterone and estrogen, or levonorgestrel and estrogen.

b) Preparations containing: desogestrel and estrogen, gestodene and estrogen, norgestimate and estrogen, or norelgestromin and estrogen.

c) Preparations containing: drospirenone and estrogen, desogestrel or lynestrenol.

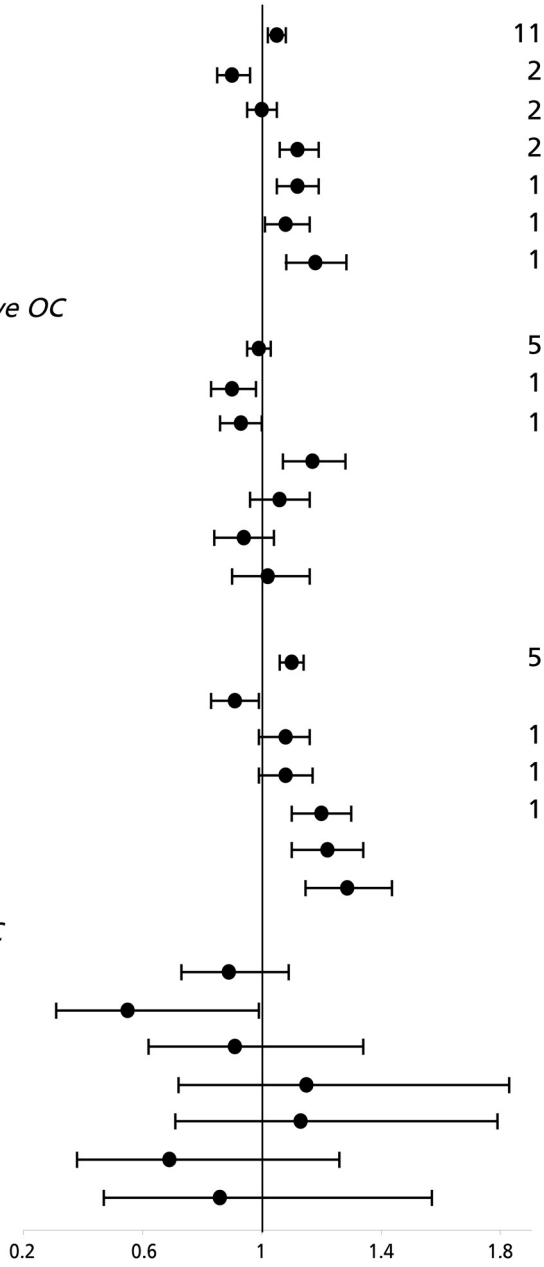
TABLE 2 – Discontinuation rates for oral contraceptives, overall and per age group

AGE GROUP	POLICY INTERVENTION COHORT (N=434 917)		POLICY CONTROL COHORT (N=489 904)		RELATIVE RISK
	Patients discontinuing	Patients in age group	Patients discontinuing	Patients in age group	
in years	n (%)[a]	n	n (%)[a]	n	RR (95%CI)
All ages	60 549 (13.9%)	434 917	55 744 (11.4%)	489 904	1.22 (1.21–1.24)
< 20	3 667 (5.8%)	63 412	3 854 (5.7%)	67 896	1.02 (0.98–1.06)
20 – 24	12 896 (13.4%)	96 055	11 805 (10.9%)	108 232	1.23 (1.20–1.26)
25 – 29	15 575 (20.0%)	78 002	14 970 (16.8%)	89 235	1.19 (1.17–1.21)
30 – 34	13 337 (19.0%)	70 257	12 859 (15.4%)	83 392	1.23 (1.20–1.26)
35 – 39	8 912 (13.0%)	68 674	7 636 (9.8%)	77 743	1.32 (1.28–1.36)
40 – 44	6 162 (10.5%)	58 517	4 620 (7.3%)	63 406	1.45 (1.39–1.50)

a) Percent refers to the percentage of discontinuing patients per corresponding age group.

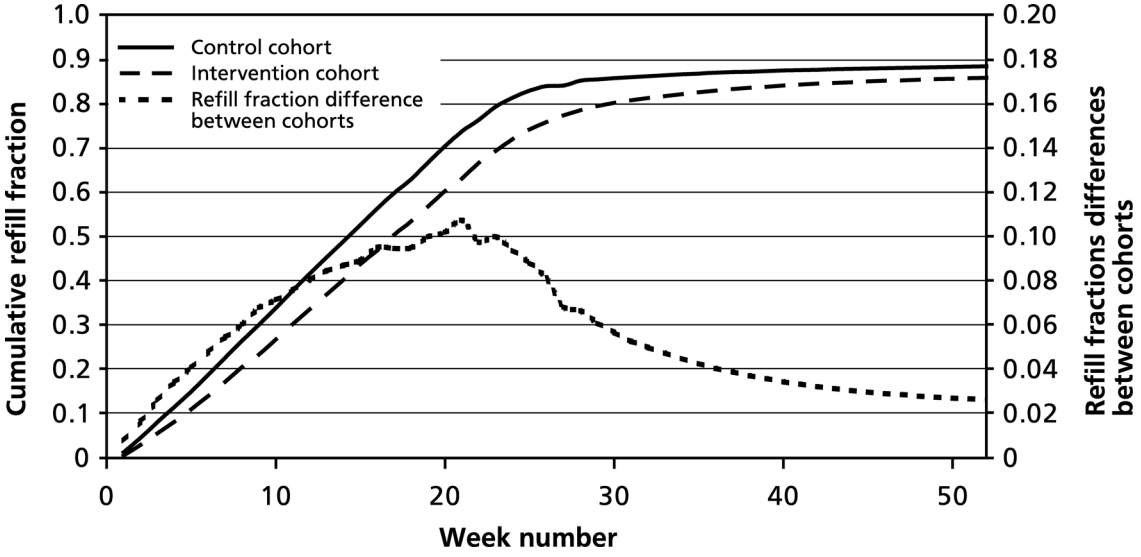
TABLE 3 – Switchers per age group and types of switch based on the price difference between the original and the new product

SWITCHERS	INTERVENTION COHORT n (%)[a]	CONTROL COHORT n (%)[a]
All switchers		
all ages	11 049 (2.5%)	11 877 (2.4%)
<20 years	2 006 (3.2%)	2 383 (3.5%)
20-24 years	2 551 (2.7%)	2 876 (2.7%)
25-29 years	2 034 (2.6%)	2 072 (2.3%)
30-34 years	1 849 (2.6%)	1 962 (2.4%)
35-39 years	1 462 (2.1%)	1 527 (2.0%)
40-44 years	1 147 (2.0%)	1 057 (1.7%)
To more expensive OC		
all ages	5 136 (1.2%)	5 867 (1.2%)
<20 years	1 131 (1.8%)	1 340 (2.0%)
20-24 years	1 225 (1.3%)	1 484 (1.4%)
25-29 years	957 (1.2%)	935 (1.1%)
30-34 years	766 (1.1%)	892 (1.1%)
35-39 years	603 (0.9%)	731 (0.9%)
40-44 years	454 (0.8%)	485 (0.8%)
To cheaper OC		
all ages	5 677 (1.3%)	5 793 (1.2%)
<20 years	858 (1.4%)	1 010 (1.5%)
20-24 years	1 275 (1.3%)	1 334 (1.2%)
25-29 years	1 034 (1.3%)	1 101 (1.2%)
30-34 years	1 039 (1.5%)	1 032 (1.2%)
35-39 years	825 (1.2%)	768 (1.0%)
40-44 years	646 (1.1%)	548 (0.9%)
To same price OC		
all ages	170 (0.04%)	215 (0.04%)
<20 years	17 (0.03%)	33 (0.05%)
20-24 years	47 (0.05%)	58 (0.06%)
25-29 years	35 (0.04%)	35 (0.04%)
30-34 years	35 (0.05%)	37 (0.04%)
35-39 years	17 (0.02%)	28 (0.03%)
40-44 years	19 (0.03%)	24 (0.04%)



Switches for which we could not establish the price difference are not shown (66 switches in intervention cohort, 2 switches in control cohort). Closed circles indicate relative risks for the intervention versus the control cohort and error bars indicate 95% confidence intervals.
a) Percent refers to the percentage of switchers per corresponding age group.

FIGURE 1 – Cumulative refill fractions for the intervention and control cohort based on a weekly analysis for 1 – 52 weeks after the index date



The primary y-axis (left side) and the closed and dashed line show the cumulative refill fractions for the control and the intervention cohort. The secondary y-axis (right side) and the dotted line depict the differences in refill fractions between the intervention and control cohort.

DISCUSSION

This study provides information about the impact of limiting reimbursement for OCs on utilisation patterns. We found that an additional 3% of patients who used OCs on the date of the policy intervention, and were affected by the reimbursement measure based on their age, discontinued the use of this drug in the following year. This signifies an increase in the discontinuation rate of 24% when compared to the discontinuation rates in the control cohort. Based on insurance claim data for the Netherlands for 2003, we estimate that the reimbursement measure has resulted in an additional 38 000 persons discontinuing the use of OCs. Whether or not these patients discontinued solely because of the change in the reimbursement status, or whether other factors played a role in the decision process is unknown. Our estimate for the discontinuation rate in this study is lower than reported in analyses using aggregate-level data in the Netherlands showing a decrease in use of up to 9%.[9]

The age group with patients <20 years was virtually unaffected by the policy intervention. In this group we found an increase in the discontinuation in 2004 compared with 2003 rates of 0.10%, possibly related to other factors, such as natural fluctuations between different years in the utilisation data. In any case, the lack of difference in the <20 years group when compared to the effect found in older patients underlines the validity of the design chosen in this study. The increase in discontinuation rates was most pronounced in the 40-44 year group, this may signify a group of women that, because of age and life-style reasons, was considering to discontinue OCs, and was further stimulated by the increased out-of-pocket costs to stop using the drug. We did not find differences in the discontinuation rates when we compared first and second generation OCs to third generation OCs. This means that, although third generation OCs were associated with an increased risk for venous thromboembolism during the study period,[10] negative information about the drug class apparently did not cause discontinuation rates for third generation OCs to be higher or the impact of the reimbursement measure to be more pronounced in users of this drug class.

When looking at switching to different products, we detected an overall increase in switching to cheaper alternatives in nearly all affected age groups. Most evidence for an increase of switching to cheaper alternatives was found in the 29-44 years age range. In the group unaffected by the policy intervention (<20 years) there was actually a small effect in the other direction: less patients switched to a cheaper alternative than in the control group.

When we compare the discontinuation and switching rates found in this study to an earlier four-year survey conducted in the Netherlands between 1990-1993, we found that our discontinuation rates in the control cohort closely matched the rates in this earlier survey (between 12-13% for three out of four surveyed years).[11] Although the four-year survey is somewhat dated, we have no reason to assume that any major changes have taken place in the possible reasons for discontinuing OCs. Therefore, we believe that our control cohort provides a useful basis for estimating the impact of the policy intervention. In contrast, the switching rate in our analysis of dispensing data was four- to fivefold lower than in the survey. This difference may be explained by the method used for measuring medication switches. In the survey this was based on self-reported changes in the previous twelve months, in our analysis we used trade product codes registered in the pharmacy.

Our analysis of the time trend of the policy effects suggests stockpiling behaviour. The fact that many patients apparently return later to fill their next prescription in the intervention compared to the control group (initially increasing difference in cumulative refill fractions, followed by a decrease) provides evidence of this. The time-course analysis further illustrates that depending on when during the follow-up time refill or discontinuation rates are calculated, differences up to a factor of five can be observed. Future policy evaluations should incorporate the proper timing of the evaluation into the design and ideally both short-term and longer-term results should be depicted for a proper understanding of a new reimbursement policy.

Using pharmacoepidemiological methods in the evaluation of pharmaceutical policies provides several advantages: observational studies can provide individual data for a large number of patients, and directly measure the primary effect of the policy intervention.[12,13] Often, this type of information is lacking from the debate. To take the Dutch example for the OC case: previous analyses were performed using highly aggregated data, were based on interviews with a small number of patients, or focused on outcomes that have only an indirect causal relationship with the discontinuation of OC reimbursement, such as the number of abortions or unplanned pregnancies. In the end, the reimbursement measure was recalled on 1 January 2008, returning OCs into the basic reimbursement package. This recall was a political decision, and was part of the coalition agreement between the three political parties that form the Dutch government that entered office in 2007. An assessment at the patient level of the effects of the earlier reimbursement restriction was not included in the decision process.

There are certain limitations that have to be considered when interpreting the results of this study. The impact of the policy measure on discontinuation rates may have been underestimated since a number of patients may be 'immune' for the reimbursement measure due to coverage by additional insurance schemes. We did not have information about the extent of insurance coverage for individual patients. Furthermore, the socio-economic status of patients was unknown. It is conceivable that, based on the reimbursement restriction, patients with lower incomes are more likely to decide to forego using OCs than patients with a higher income. Therefore, the discontinuation rates may be higher than the average of the cohort in this subgroup. We were not able to establish whether discontinuation signified 'true' discontinuation or was caused by

switching to alternative contraceptive methods such as intrauterine devices or barrier methods. Furthermore, we focused on discontinuation based on the first prescription after the index date, which may lead to an underestimation of the true discontinuation rate.

In conclusion, pharmacoepidemiologic evaluations of policy interventions can provide useful information to fuel an evidence-based debate on the impact of policies. In this study, the discontinuation of the reimbursement of OCs in women over 21 years of age in the Netherlands led to a 24% increase in the discontinuation rate for this drug, but this was not as extensive as reported in other publications. We detected an increase of switching to cheaper alternatives in most age groups. However, in absolute terms this increase was relatively small. Finally, whenever a policy evaluation is considered, the time period for which the data are collected and an assessment of the impact of the policy intervention is made should be chosen with care.

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chapter 3.2

chapter 3.2

Variable access to clopidogrel in a harmonised EU market

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ABSTRACT

Objectives

This study focuses on the different national coverage and reimbursement strategies and their consequences for access to clopidogrel, a drug with a central European Union (EU) registration. Our objectives are 1) to assess whether changes in reimbursement policies in EU member states influenced clopidogrel prescribing; and 2) to determine whether clopidogrel-specific policy characteristics, general characteristics of the health system, or indicators for the amount of cardiovascular care delivered were associated with the level of clopidogrel prescribing.

Methods

Data were collected in Austria, Belgium, Denmark, Germany, Hungary, Portugal, Slovenia, The Netherlands, and the United Kingdom (England). Utilisation rates were expressed as defined daily doses (DDDs)/1000 persons/day. To determine whether changes in reimbursement policies influenced clopidogrel utilisation, a segmented linear regression approach was used.

Results

Clopidogrel prescribing varied widely in the studied countries, from 2.76 (The Netherlands) to 6.83 (Belgium) DDDs/1000 persons/day (March 2005). Six countries had therapeutic indication restrictions to clopidogrel use. Health system characteristics did not explain variation in clopidogrel prescribing.

Conclusion

A disconnect will be indicated in this study between the concept of a harmonised EU pharmaceuticals market and the reality in an individual member state. Although clopidogrel was centrally registered in the EU, policy measures at the national level result in different roles in clinical practice for this drug.

INTRODUCTION

Clopidogrel (Plavix®, Sanofi-Aventis, Paris, France) is a thienopyridine antiplatelet drug that prevents thrombocyte aggregation by limiting the activation of the platelet GpIIb/IIIa complex through selective antagonism of an adenosine 5'-diphosphate receptor. The mechanism of action of clopidogrel is different from other antithrombotic drugs such as acetylsalicylic acid, which inhibits the formation of the prothrombotic compound thromboxane A2.[1]

The daily costs for clopidogrel are much higher than for most older antithrombotics. In 2005, clopidogrel generated about US$6 billion in sales, making it the second best-selling drug worldwide.[2] Since 1995, pharmaceutical products with a new active substance can be assessed by the European Medicines Agency (EMEA) for the whole European Union (EU). Clopidogrel was authorised by the European Commission for all EU member states on July 15, 1998. The initial indication of clopidogrel was "the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischemic stroke, and peripheral arterial disease". Four years later, on September 9 2002, the European Commission approved a new indication: "the treatment of acute coronary syndrome in combination with acetylsalicylic acid", mainly based on evidence from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study.[3] Both of these indications are recorded in the single Summary of Product Characteristics (SmPC) that exists for the whole EU.

Nevertheless, the organisation and financing of the health system, and with it the provision of pharmaceuticals to patients, falls within the competence of each individual member state. As a consequence of this, utilisation of health-care resources may vary widely between EU countries.[4-6] At this moment, little is known about the relationship between different national coverage and reimbursement strategies and their consequences for access to, and utilisation of, individual drugs in the EU. The present study focuses on this variation and its national regulatory determinants related to coverage and reimbursement of clopidogrel, a drug that has been the target for government interventions in many countries because of its relatively high per unit costs and total budget impact.

Our aims in this study were to assess whether changes in reimbursement policies in nine EU member states influenced the utilisation patterns of clopidogrel, and

to find out whether specific policy characteristics related to clopidogrel, general characteristics of the health system, or indicators for the amount of cardiovascular care delivered were associated with the level of clopidogrel prescribing.

TABLE 1 – Data sources

COUNTRY	DATA SOURCE	TYPE	PERIOD COVERED	COVERAGE 2005 (%)[a]
Austria	Austrian Sickness Fund	reimbursement	Oct 98 – Mar 05	7.7 million (95.0%)
Belgium	FARMANET	reimbursement	Mar 01 – Oct 05	10.4 million (100.0%)
Denmark	OPED	dispensing	Oct 98 – Jul 05	472 000 (8.8%)
Germany	DAPI	dispensing	Jan 03 – Aug 05	70.4 million (85.0%)
Hungary	HNNFA	reimbursement	Jan 01 – Oct 05	10.1 million (100.0%)
Netherlands	SFK	dispensing	Jan 98 – Sep 05	15.0 million (91.7%)
Portugal	CEFAR	dispensing	Jan 02 – Sep 05	10.4 million (100.0%)
Slovenia	Health Insurance Institute of Slovenia	reimbursement	Jul 00 – Oct 05	2.0 million (100.0%)
United Kingdom (England)	PACT	reimbursement	May 01 – Sep 05	50.4 million (89.0%)

a) Coverage in number of people (% of total population).

METHODS

Nine EU member states have been included in this study: Austria, Belgium, Denmark, Germany, Hungary, The Netherlands, Portugal, Slovenia and the United Kingdom (England). These countries participate in the PILLs (Post-Innovation Learning Cycle for Pharmaceuticals) research network, an international network involved in the study of the effects of pharmaceutical policies on drug use. Table 1 shows an overview of the sources used for the extraction of utilisation data. Of the nine sources, four contained dispensing data and five used reimbursement data to capture drug utilisation. All data sources provided information on the prescribing of clopidogrel in ambulatory care; hospital prescribing was not covered. Eight data sources covered 85% or more of the total population. The Danish Odense Pharmacoepidemiological Database

(OPED) database (coverage 8.8%) is a pharmacoepidemiological research database. This database provides a representative sample of the population of Denmark with respect to drug utilization.[7,8] Data were available on a monthly basis, except for the Austrian data, which were provided on a quarterly basis.

We extracted utilisation data for products containing clopidogrel for the period from 1998 to 2005. Utilisation was expressed as defined daily doses (DDDs)/1000/persons/day. The DDD is a dosage measure determined by the World Health Organisation (WHO); it is based on the average daily maintenance dose in adults. For clopidogrel, the DDD is 75 mg.[9] Utilisation rates were calculated using the mid-year number of persons covered by a data source, or the mid-year population of a country according to the national statistics agency.

We collected information about three possible determinants for clopidogrel prescribing: specific policy characteristics related to clopidogrel, general characteristics of the health system, and measures for the amount of cardiovascular care delivered.

Specific policy characteristics related to clopidogrel were collected per country using a questionnaire filled in by country representatives. For each country, we requested information about the restrictions on reimbursement in national insurance policies, position statements by professional associations, and other important policy events. Based on these specific policy characteristics, we classified each country as having either 'high' or 'low' access barriers to clopidogrel prescribing. The index date for the assignment was March 2005, the most recent date for which utilisation data were available for all countries.

When available, the following health system characteristics were retrieved per country: gross domestic product (GDP) per capita (2003), spending on pharmaceuticals in purchasing power parities (2003), pharmaceutical spending as a percentage of total health expenditure (2003), and the number of practicing physicians (2003).

As measures for the amount of cardiovascular care delivered, we collected, depending on availability, standardised death rates for ischemic heart disease (2002), disability from heart disease in disability adjusted life-years (2003), and the number of coronary procedures per 100 000 inhabitants (2003).

Information about the health system characteristics and measures for the amount of cardiovascular care delivered were retrieved from Eurostat,[10] the Organisation for Economic Cooperation and Development,[11] and WHO.[12]

TABLE 2 – Clopidogrel utilisation per country and access barriers in relation to GDP, spending on pharmaceuticals in purchasing power parities, pharmaceutical spending as a percentage of total health expenditure, number of practicing physicians, standardised death rates for ischemic heart disease, disability from heart disease in Disability Adjusted Life Years and the number of coronary procedures per 100 000 inhabitants

COUNTRY	CLOPIDOGREL UTILISATION (MARCH 2005) in DDDs/1000 persons/day)	LEVEL OF ACCESS BARRIERS (RESTRICTIONS)[a]	GDP IN PURCHASING POWER STANDARDS[b]	PHARMACEUTICAL SPENDING IN PPPs (USD, 2003)[11]	PHARMACEUTICAL SPENDING AS % OF TOTAL HEALTH EXPENDITURE (2003)[11]	PRACTICING PHYSICIANS/1000 persons (2003)[11]
Belgium	6.83	High (CP)	117.7	NA	NA	3.9
UK (England)	5.47	Low (CP)	116.5	NA	NA	2.2
Germany	5.15	Low (CP)	109.3	436	14.6	3.4
Portugal	5.13	Low (-)	71.3	NA	NA	3.3
Denmark	3.83	High (RI, CP)	124.2	272	9.8	2.9
Austria	3.21	High (RI, CP)	122.5	389	16.9	3.4
Hungary	3.20	High (RI, RP, CP)	61.4	306	27.8	3.2
Slovenia	2.99	High (RI, CP)	80.6	NA	NA	NA
Netherlands	2.76	High (RI)	124.2	340	11.4	3.1

(TABLE 2 CONTINUED)

COUNTRY	SDRs ISCHEMIC HEART DISEASE, AGE STANDARDISED DEATH RATES/100 000 (2002)[11]		DISABILITY FROM HEART DISEASE IN DALYs LOST/1000 PERSONS(2003 or MOST RECENT)[12]	CORONARY PROCEDURES/100 000 PERSONS (2003)[11]		
	Male	Female		Angioplasties	Coronary bypasses	Revascularisations
Belgium	NA	NA	5	332	159	NA
UK (England)	174.7	84.1	7	99	56	145
Germany	163.0	84.6	6	270	87	342
Portugal	83.8	42.2	5	66	22	82
Denmark	148.0	74.5	5	157	60	205
Austria	166.8	93.0	6	175	54	234
Hungary	276.3	162.9	13	189	125	251
Slovenia	NA	NA	6	NA	NA	NA
Netherlands	105.5	48.7	5	93	53	137

GDP = gross domestic product; PPPs = Purchasing Power Parity; NA = not available; DALYs = Disability Adjusted Life Years

a) Restrictions: CP = Co-Payment; RI = Reimbursed only for certain Indications; RP = Reimbursed only when Prescribed by certain specialties.

b) EU-25 AVERAGE = 100 (2005).[10]

Statistics

We analysed the data using two methods: a longitudinal and a cross-sectional analysis. Our goal in the cross-sectional analysis was to determine whether changes in reimbursement policies could be linked to change-points in the utilisation trends of clopidogrel. For this purpose we used an algorithm that cuts each time series into segments by fitting optimal piecewise least squares linear regressions. A change-point was defined as a statistically significant difference in the slope for the two consecutive segments. We used the segmentation with the minimal number of possible change-points.

The segmentation algorithm is based on dynamic programming.[13] We assumed a linear relation between drug utilisation and calendar time within each segment. To justify this assumption, we fitted only a linear regression line within a segment under the following conditions:

1. There is no systematic structure in the plot of residuals of the fitted regression versus time using the smoothing spline-line for residuals in the general additive model;
2. Residuals have constant variance over time based on a Shewhart control chart with a moving standard deviation parameter and a sliding interval length of 8;
3. The residuals are not autocorrelated (using an autocorrelation plot with a 95% confidence band).

In the cross-sectional analysis, Pearson's r-test for continuous variables and Spearman's rank-test for noncontinuous variables were used to calculate the associations between general characteristics of a country or high/low access barriers to prescribing and clopidogrel utilisation. March 2005 was the index date for these calculations; a p-value less than 0.05 was deemed statistically significant.

RESULTS

The utilisation rate of clopidogrel in March 2005, the most recent date for which we had data available for all countries, varied strongly from 2.76 DDDs/1000 persons/day for the Netherlands to 6.8 DDDs/1000 persons/day for Belgium (Table 2).

The reimbursement restrictions that were in place in the studied countries in March 2005 are shown in Table 2. All national insurance policies reimbursed

clopidogrel for the indications mentioned in the EMEA SmPC. The use of clopidogrel after elective stent placement, not an official indication in the SmPC, was reimbursed in all countries except for Belgium, Hungary, and The Netherlands (Tables 2 and 3). Based on the existence of restricted indications and the related (pre-)approval of a prescription, we categorised six countries as having 'high' access barriers to prescribing (Austria, Belgium, Denmark, Hungary, The Netherlands, and Slovenia) and three countries as having 'low' access barriers to prescribing (Germany, Portugal, and the United Kingdom [England]).

In Figures 1A en B, the utilisation of clopidogrel over time is shown as 3-month moving averages for countries with 'low' access barriers and 'high' access barriers, respectively. For seven countries, data were available from the start of marketing of clopidogrel. For two countries (Germany and the United Kingdom [England]), data were only available from a later date onward (May 2002 and January 2003, respectively).

Statistically significant change-points in the utilisation trend detected with the segmentation algorithm within a 3-month time window of changes in the reimbursement status are represented in Figures 1A en B by a closed symbol. Open symbols denote a nonsignificant result. The segmentation algorithm shows that, except for the Belgian reimbursement changes and the general increase in copayments in Germany, reimbursement measures had a significant impact on the utilisation time series. In Slovenia, a more detailed reimbursement restriction statement was released on May 10 2004, to manage resources; this is the likely cause of abrupt change in the trend around this date. In Austria, an 84-unit package of clopidogrel was removed from the positive reimbursement list on January 1 2005, in favor of a 1-month package; this may have caused a very large, but temporary, decrease in the number of DDDs dispensed. Although reimbursement was extended in the Netherlands in July 2004, the time trend for clopidogrel utilisation decreased. The between-month variation in the clopidogrel utilisation data for Germany was very high; this decreased the sensitivity of our segmentation algorithm.

Although in Figures 1A en B the utilisation rates are generally higher in countries with low access barriers to prescribing, the association between the level of access barriers and utilisation in March 2005 was not statistically significant (rho = 0.127).

TABLE 3 – Specific indication restrictions to the reimbursement of clopidogrel (March 2005)

COUNTRY		REIMBURSED INDICATIONS FOR CLOPIDOGREL
Austria	(AU)	▪ Reduction of atherosclerotic events in patients with a history of atherosclerosis defined by either ischemic stroke/transient ischemic attack (4 days to 6 months previously), myocardial infarction (max. 35 days previously), or documented peripheral arterial occlusive disease when treatment when acetylsalicylic acid has failed; ▪ After acute coronary syndrome (unstable angina pectoris or non Q-wave myocardial infarction without typical ST-elevation with elevates troponin or CPK and clinical symptoms) without further risk factors for atherosclerosis for 3-6 months in combination with acetylsalicylic acid; ▪ In combination with acetylsalicylic acid for 9-12 months post Acute Coronary Syndrome for high-risk patients (reinfarction and/or documented atherosclerosis in more than one vascular area) or post PTCA (and stent implantation).
Belgium	(BE)	Second line treatment in hypersensitvity for acetylsalicylic acid (history of haemorrhage, ulcus, asthma, Quincke-oedema or hypotension), or in the case of thromboembolic accidents with clinical sequelae during treatment with acetylsalicylic acid, in the following cases: Secondary prophylaxis after an ischemic cerebrovascular accident, secondary prophylaxis after a myocardial infarction, prophylaxis in diagnosed peripheral arterial disease.
Denmark	(DK)	▪ Ischemic heart disease or peripheral arterial insufficiency with intolerance to acetylsalicylic acid; ▪ Secondary prophylaxis of ischemic cerebral apoplexy and/or transient cerebral ischemia with intolerance to acetylsalicylic acid and/or dipyridamole; ▪ Unstable angina or acute non-ST elevation myocardial infarction and treatment is commenced within 24 hours after the first symptom as a supplement to acetylsalicylic acid; ▪ After revascularisation treatment in coronary vessels or peripheral arteries by the insertion of stents.
Germany	(GER)	No restrictions.
Hungary	(HU)	Can only be prescribed with 90% reimbursement by a haematologist, specialist in internal medicine, neurologist, cardiologist, or general practitioner for the following indications: ▪ Resistance, intolerance, allergy to acetylsalicylic acid and ticlopidine therapy; ▪ In combination with acetylsalicylic acid, if neither of them are effective alone in the prevention of platelet aggregation.

COUNTRY (Table 3 continued)		REIMBURSED INDICATIONS FOR CLOPIDOGREL
Netherlands	(NL)	▪ After a myocardial infarction or ischemic cerebrovascular accident or diagnosed peripheral arterial disease, when treatment with acetylsalicylic acid is not possible due to hypersensitivity or another absolute contraindication for acetylsalicylic acid; ▪ The treatment of Acute Coronary Syndrome without ST-segment elevation during six months in combination with acetylsalicylic acid.
Portugal	(PT)	No restrictions.
Slovenia	(SLV)	Secondary prevention of cerebrovascular and cardiovascular complications, when the use of acetylsalicylic acid is contraindicated. In combination with acetylsalicylic acid for coronary heart disease patients with an inserted stent.
United Kingdom (England)	(UK)	No restrictions.

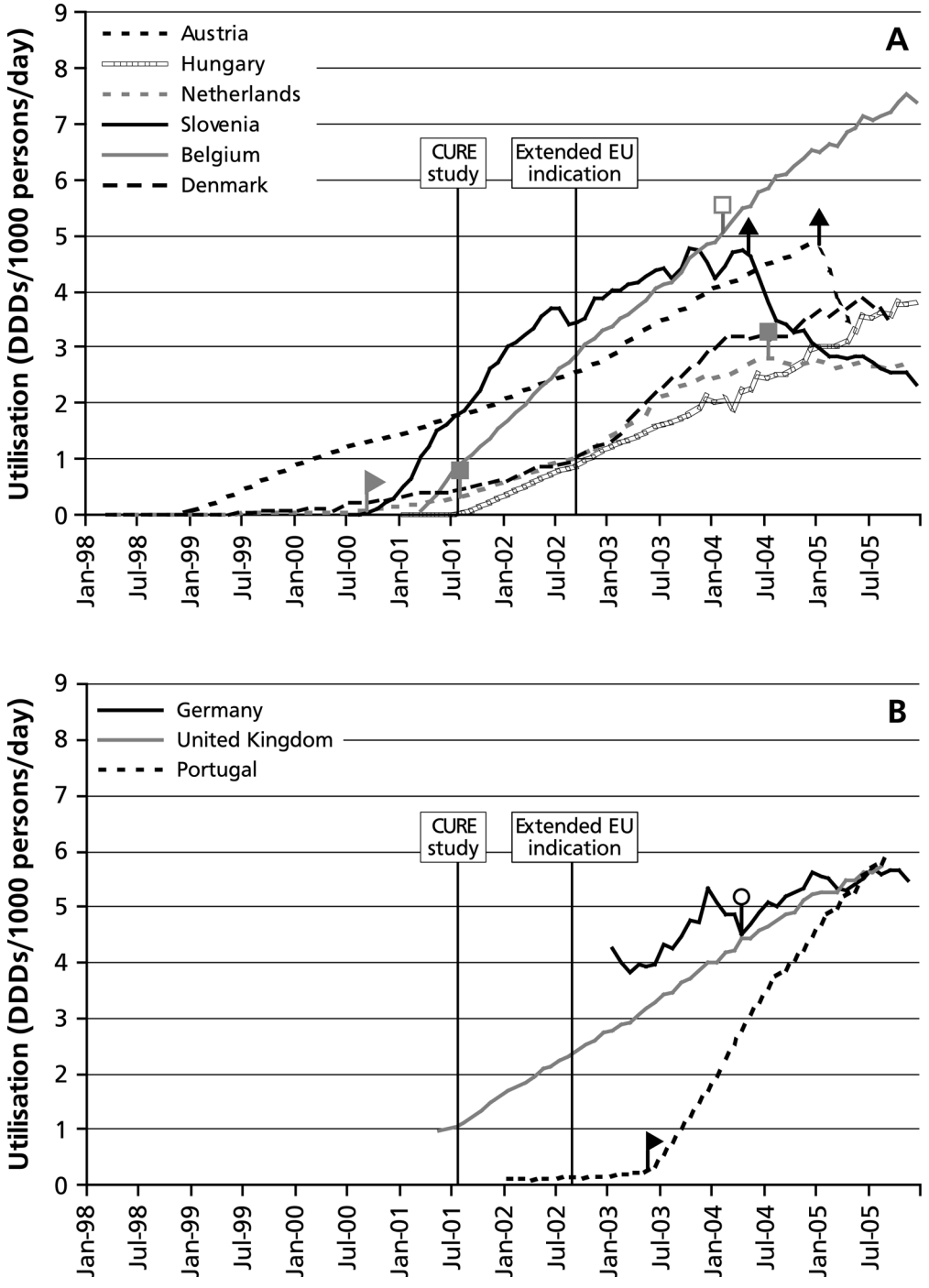
None of the available general characteristics of a country had a statistically significant association with the utilisation of clopidogrel in March 2005. Also, the indicators for the amount of cardiovascular care delivered in each country were not statistically significantly associated with the amount of clopidogrel prescribing.

DISCUSSION

In this study, we observed large between-country variation in clopidogrel utilisation, as well as in the reimbursed indications for clopidogrel. General characteristics, such as GDP per capita and the number of practicing physicians, could not explain these differences. Furthermore, the amount of cardiovascular care delivered (as measured by, for example, the number of coronary bypasses, revascularisations or angioplasties per 100 000 inhabitants) was also not associated with clopidogrel prescribing. Apparently, other factors determine the utilisation of clopidogrel, such as reimbursement measures or culture. A qualitative assessment of the data shows that the existence of reimbursement restrictions may be a predictor for low clopidogrel utilisation, although we did not find statistically significant differences to substantiate this claim. Only the Belgian data rebut this conclusion. The reimbursement policy in Belgium looks fairly strict on paper; however, it does not translate into lower utilisation rates. In this context, it is interesting to note that Belgium also has the highest number of practicing physicians per 1000 persons and the highest number of coronary interventions per capita, which may also explain our finding.

To determine whether a reimbursement event had a significant impact on the trend of the utilisation time series, we made use of a segmentation algorithm. In most countries where changes were made to the reimbursement policy, this resulted in detected changes to the utilisation time series, which are also visible in Figures 1A en B. An algorithm such as this one could also be used for other purposes in pharmacoepidemiology and drug utilisation research. Although a certain amount of follow-up is needed for the algorithm to function, making it less useful for rapid monitoring, it can be useful for longitudinal comparisons. Furthermore, it can be applied to a variety of data series, not restricted solely to drug use.

FIGURE 1 - Utilisation of clopidogrel 1998–2005 in countries with low access barriers (A) and high access barriers (B)



▶ = start of reimbursement; ■ = extended reimbursement; ▲ = change in reimbursement rules (no extension); ● = general increase in co-payments. Closed symbols denote a significant result detected with the segmentation algorithm, open symbols a non-significant result.

A topic increasingly discussed in both the scientific and the lay press is the tension between the reimbursed, or labeled, indication of a drug and that what is portrayed as best practice. The extensive debate in the United Kingdom about the reimbursement of trastuzumab in early breast cancer recently highlighted this issue.[14,15] The clopidogrel case is relevant in this discussion as well. Various professional organisations have argued that there is sufficient evidence for the use of clopidogrel after the placement of a stent.[16,17] Nevertheless, this is not an officially registered EMEA or U.S. Food and Drug Administration indication. In this study, three countries (The Netherlands, Belgium, and Hungary) do not reimburse clopidogrel for this indication, whereas the other six do. This illustrates the sometimes contradictory process of, on the one hand, harmonisation at the community level, with a single SmPC for products in a single European market, and, on the other hand, the (political) realities at the national level, where the actions of various parties, such as governments and insurers, create a diverse range of policies and restrictions to prescribing. Often, policymakers have to position themselves between what the market authorisation holder has registered as the therapeutic indication with authorities such as EMEA, and what is additionally regarded as the proper place for a therapy in the scientific literature. The latter results in, by definition, off-label prescribing.[18] This difficult choice requires a thoughtful weighing of the value of a new drug therapy and the financial burden that a health-care system can carry.[19] International comparisons of cost-effectiveness may also add to this decision process. In this study, we have shown large variation in the use and uptake of clopidogrel. These findings are also important for the conduct and interpretation of cost-effectiveness studies for this drug.

When interpreting the results of this study, there are certain limitations that have to be taken into account. First, data originated from several types of sources, both dispensing data (four countries) and reimbursement data (five countries) were included. Therefore, a small percentage of drug utilisation may not have been captured by the reimbursement data sources (e.g. out-of-pocket payments or nonreimbursed use). Furthermore, with the aggregate data we used in this study, it is not possible to determine for which indication a drug was prescribed. Therefore, we are not able to detect shifts at the patient level. Moreover, to what extent 'off-label' prescribing of clopidogrel varied (e.g. after stent placement) could not be determined. Another determinant that could explain international

variation is different levels of promotional activities by the market authorisation holder. No data, however, were available to us to investigate this variable. Furthermore, we assumed that the national reimbursement rules are a prime driver for clinical practice; we believe this is reasonable in the types of health systems seen in the studied countries. Nevertheless, cultural differences and other regulatory and morbidity aspects that we were not able to include in our analysis undoubtedly have an impact as well. Unfortunately, these aspects are generally difficult to quantify and analyse in a multicountry study. Therefore, this study is not directed at identifying which country has the 'best' policy with regard to clopidogrel. What is optimal for each country depends on various factors such as available resources, the structure of the health system, and the relative prices of all available inputs. Finally, the countries in this study represent different geographic regions of Europe, different health-care systems, and both 'old' and 'new' member states of the EU. This can make results from one country difficult to translate to the realities of another health-care system. These differences, however, between health systems are also the strength of this study, as they provide insight into the extent of variation that exists within the EU. In the future, multicountry studies should strive for the inclusion of more EU member states for multilevel studies on the effects of national coverage and reimbursement strategies on the usage patterns of drugs.

In conclusion, we observed large variation between European countries in the utilisation of clopidogrel. As could be expected, high utilisation of clopidogrel was more often seen in countries with few restrictions to reimbursement, although this association was not statistically significant. Other studied characteristics of the country or health system offered little explanation for the differences in the utilisation of clopidogrel. Furthermore, with regard to the use of clopidogrel after stent placement (which is not an EMEA-authorised indication for clopidogrel), the reimbursement coverage varied widely across the studied countries. This indicates a disconnect between the concept of a harmonised EU market with a single SmPC and the reality of the clinical role of, in this case, clopidogrel in the individual member states. The various national interpretations about the proper place of a drug in relation to its labeled indications and available scientific evidence is a topic that should feature prominently on future European public health agendas.

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chapter 3.3

Between country variation in the utilisation of antihypertensive agents: guidelines and clinical practice

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ABSTRACT

Introduction

Variation in antihypertensive drug utilisation and guideline preferences between six European countries (Denmark, Finland, Germany, Norway, Sweden, The Netherlands) was investigated. Our objectives were to compare between-country variability in utilisation per class of antihypertensive agents and to assess guideline preferences in relation to actual use.

Antihypertensive consumption data (2003) was retrieved.

Methods

We classified antihypertensive agents using Anatomical Therapeutic Chemical codes: C02CA – alpha-blockers (AB), C03A – thiazide diuretics (TD), C07AB – beta-blockers (BB), C08CA – dihydropyridine calcium antagonists (CA), C09A/C09BA/C09BB – ACE-inhibitors + combinations (AI), and C09C/ C09D – angiotensin II receptor blockers + combinations (AT2). For each class, Defined Daily Doses (DDDs)/1000 persons/day and share (%) of total antihypertensive utilisation was calculated. Per class, relative standard deviations (RSD) across countries were computed. Current hypertension guidelines were requested from national medical associations.

Results

Total antihypertensive utilisation varied considerably, ranging from 152.4 (The Netherlands) to 246.9 (Germany) DDDs/1000 persons/day. RSD was highest for TD (106.2%) and AB (93.6%). Where guidelines advocated TDs (Norway, The Netherlands), TD utilisation was below (Norway) or just above (The Netherlands) median TD use. Guidelines recommended TD (Norway, The Netherlands), TD/BB/AI (Finland, German Physicians Association) or TD/BB/CA/AI/AT2 (Denmark, German Hypertension Society), Sweden had no recent national guideline.

Conclusion

In conclusion, antihypertensive utilisation patterns varied largely across these six countries, in absolute and relative terms. Furthermore, guidelines seem disconnected from clinical practice in some countries, and none of the guidelines discuss current utilisation. Whether this reflects a need for change in prescribing or re-evaluation of guidelines warrants further research.

INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular disease. In recent decades, the management of hypertension has improved markedly, contributing to a strong decrease in death rates in North America and Western Europe.[1,2] Improvements in reducing this risk factor can be attributed to lifestyle modifications and better detection, but an increase in the use of effective pharmacological therapies has also played an important role.

The widespread use of antihypertensive agents, the public health relevance of hypertension as a risk factor, and the costs involved have made this drug class a topic in drug utilisation research and 'evidence based medicine' from early on.[3,4] Moreover, many national medical associations and international organisations aim to promote certain prescribing behaviour by publishing and implementing 'evidence based' guidelines.

Although international differences in the prevalence of hypertension have been the subject of several studies,[5,6] between country differences in drug utilisation and guideline preferences are less well-documented. Therefore, our objective in this study was to evaluate, within the class of antihypertensive agents, the variation of drug utilisation between six Northern European countries by using a relative standard deviation measure and to assess guideline preferences in relation to current use.

METHODS

We defined six classes of antihypertensive agents based on Anatomical Therapeutic Chemical (ATC) codes, as determined by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology,[7] namely: alpha-blockers (C02CA), thiazide diuretics (C03A), selective beta-blockers (C07AB), dihydropyridine calcium antagonists (C08CA), ACE-inhibitors + combinations (C09A/C09BA/C09BB) and angiotensin II receptor blockers + combinations (C09C/C09D). We only included these drug classes in this study, since we considered them to be the most important classes for the treatment of (uncomplicated) hypertension, and for which hypertension will be the main indication within the class. For example, other centrally acting compounds were considered obsolete or used for specific types of hypertension

TABLE 1 – Characteristics of countries

	DENMARK	FINLAND	GERMANY	NORWAY	SWEDEN	NETHERLANDS
Population (millions)	5.4	5.2	82.5	4.6	9.0	16.2
Population aged 65 years and over (%)	15	16	18	15	17	14
GDP per capita (US Dollar)	30 733	28 455	27 094	37 017	28 881	30 315
Health expenditure as a share of GDP (%)	9.0	7.4	11.1	10.3	9.4	9.8
Pharmaceutical spending (% of all health spending)	9.8	16.0	14.6	9.4	12.6	11.4
Pharmaceutical spending per capita (US Dollar PPP)	272	339	436	341	340	340
Ischemic Heart disease (Standardised Death Rates per 10 000 persons)						
- males	148.0	223.9	163.0	148.0	162.6	105.5
- females	74.5	108.9	84.6	67.6	77.6	48.7
Cerebrovascular disease (Standardised Death Rates per 10 000 persons)						
- males	63.2	64.4	61.3	58.5	59.0	57.9
- females	51.9	53.6	47.9	46.8	48.1	47.5

GDP = Gross Domestic Product; PPP = Purchasing Power Parity
All data are for 2003. Source: OECD Health Data 2005.[8]

TABLE 2 – Sources of utilisation data and guideline preferences for first choice antihypertensive agents in uncomplicated hypertension (shaded boxes)

COUNTRY	UTILISATION DATA SOURCE	DATA TYPE	GUIDELINE SOURCE	YEAR	TD	BB	AI	CA	AT2
Denmark	Danish Medicines Agency	Dispensing	Danish Hypertension Society	2004	■	■	■	■	■
Finland	National Agency for Medicines	Wholesaler	Finnish Medical Society	2002	■	■	■		
Germany	Sick Fund		1. German Physicians Association	2004	■	■	■		
	(Arzneiverordnungsreport 2004)	Reimbursement	2. Hypertension Union	2003	■	■	■	■	■
Norway	Institute of Public Health	Wholesaler	College of General Practitioners	2000	■				
Sweden	Apoteket	Dispensing	— (last national guideline: 1993)	—					
Netherlands	Health Care Insurance Board	Reimbursement	College of General Practitioners	2003	■				
Europe	NA	-	European Society for Hypertension	2003	■	■	■	■	■
United States	NA	-	JNC-7	2003	■				
Worldwide	NA	-	WHO/ISH	1999	■	■	■	■	■

TD = thiazide diuretics; BB = beta-blockers; AI = ACE-inhibitors; CA = calcium antagonists; AT2 = angiotensin II receptor blockers; NA = not applicable; JNC-7 = seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; WHO = World Health Organisation; ISH = International Society for Hypertension

(e.g. hypertension during pregnancy). For non-selective beta-blockers, and non-dihydropyridine calcium channel we assumed, based on current evidence and guidelines, that these are primarily prescribed for other indications, such as angina pectoris or cardiac arrhythmias.

Six Northern European countries were selected for this analysis: Denmark, Finland, Germany, Norway, Sweden and The Netherlands. These countries are comparable in terms of a variety of factors, including demographic characteristics and GDP per capita (Table 1).[8,9]

We collected drug utilisation data for the six included countries for the year 2003 from different public sources, an overview of these sources is given in Table 2. Drug utilisation was captured using either reimbursement data (2 countries), wholesaler figures (2 countries), or dispensing information (2 countries). All sources report drug use as Defined Daily Doses (DDDs), a dosage measure developed by the WHO. For all countries except Germany the reported data were estimates for the whole population. The German data reported drug consumption of patients insured through the sick fund (Gesetzliche Krankenversicherung), consisting of 70.42 million people, or about 85.3% of the total German population in 2003.

Utilisation rates were calculated as DDDs per 1000 persons per day, a measure widely used in drug utilisation research. We computed these rates on the basis of the average population in a year as reported by the national statistics agency of a country, or, in the German case, based on the number of persons insured through the sick fund.

The level of between-country variation in drug utilisation was calculated for each class of antihypertensive agents across the countries with a relative standard deviation (RSD) measure, defined as:

$$100 \times \frac{\text{Standard deviation of class utilisation as \% of total antihypertensive use}}{\text{International average of class utilisation as \% of total antihypertensive use}}$$

A large RSD value indicates a large variation in relative usage share between countries. A similar measure was also used elsewhere to assess variation in drug utilisation between countries.[10]

We retrieved general practice hypertension guidelines from national (medical) associations. We screened each guideline for the recommended first choice drug(s) in patients with uncomplicated hypertension (i.e. in adults with no co-

TABLE 3 – Utilisation of antihypertensives in DDDs/1000 persons/day (% of total utilisation)

DRUG CLASS	DENMARK	FINLAND	GERMANY	NORWAY	SWEDEN	NETHERLANDS
TOTAL	*174.60 (100.0)*	*200.56 (100.0)*	*246.93 (100.0)*	*178.65 (100.0)*	*169.15 (100.0)*	*152.37 (100.0)*
Alpha-blockers	1.60 (0.9)	0.47 (0.2)	3.59 (1.5)	7.80 (4.4)	1.50 (0.9)	2.20 (1.4)
Thiazide diuretics	43.70 (25.0)	4.84 (2.4)	9.24 (3.7)	4.95 (2.8)	13.12 (7.8)	10.32 (6.8)
Selective beta-blockers	19.70 (11.3)	48.39 (24.1)	47.34 (19.2)	30.20 (16.9)	42.00 (24.8)	32.56 (21.4)
Dihydropyridine calcium antagonists	35.50 (20.3)	39.04 (19.5)	35.52 (14.4)	39.70 (22.2)	33.84 (20.0)	27.25 (17.9)
ACE-inhibitors + combinations	47.10 (27.0)	78.83 (39.3)	108.68 (44.0)	49.60 (27.8)	53.18 (31.4)	55.02 (36.1)
Angiotensin II receptor blockers + combinations	27.00 (15.5)	28.99 (14.5)	42.56 (17.2)	46.40 (26.0)	25.50 (15.1)	25.01 (16.4)

DDDs = Defined Daily Doses; ACE = angiotensin converting enzyme

morbidities or other special circumstances), and it was determined whether or not the guideline discussed current utilisation of antihypertensive agents in the respective country. For comparison, we also retrieved the WHO/International Society for Hypertension (ISH) guideline, the guideline of the European Society of Hypertension and the United States guideline from the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).

RESULTS

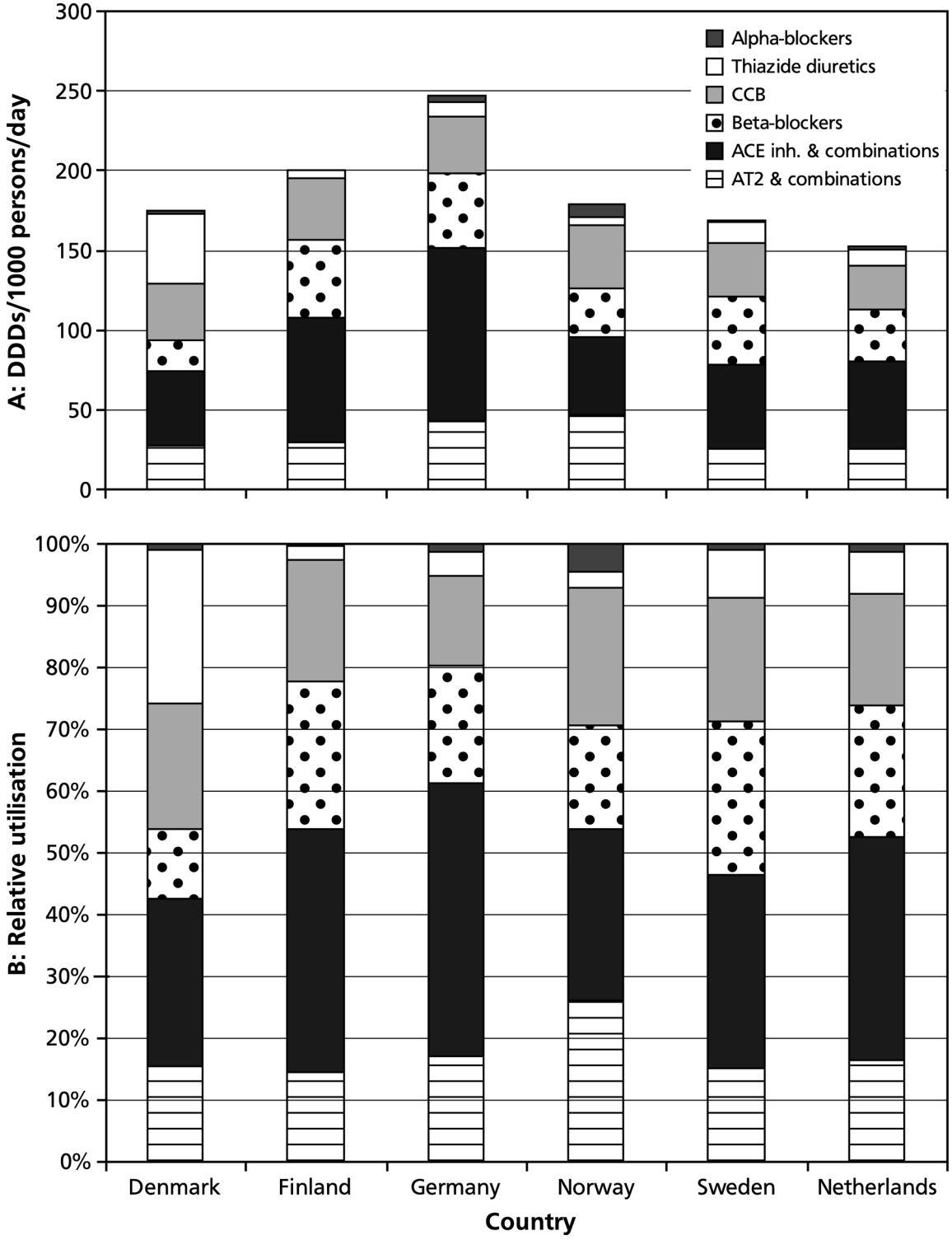
The calculated utilisation rates of antihypertensive drugs are shown in Table 3. The absolute utilisation rates of antihypertensive agents ranged from 152.4 to 246.9 DDDs/1000 persons/day for the Netherlands and Germany respectively, a difference of 62% (Figure 1A). The relative consumption of antihypertensive classes as a percentage of total antihypertensive consumption, based on DDDs, is shown in Figure 1B. The figure shows that in all countries ACE inhibitors & combinations are the primary drug class used, relative use of thiazide diuretics use shows large variation, ranging from 25.0% of all antihypertensives in Denmark to 2.4% in Finland. The Finnish data also show a relatively low use of beta-blockers. Furthermore, Norway has a higher utilisation of alpha-blockers and angiotensin II receptor blockers compared to the other countries.

When relative standard deviations were calculated, RSDs varied from 14.1% for dihydropyridine calcium channel blockers to 106.2% for thiazide diuretics (Figure 2).

Thiazide diuretics and alpha-blockers remain the classes with the highest variation even when the two extreme values with regards to thiazide or alpha-blocker use, Denmark and Norway, were excluded from the analysis.

Guideline preferences for first choice antihypertensive agents in uncomplicated hypertension in the six countries are depicted in Table 2. With respect to the preferences of the guidelines we discerned three groups. First, in the Dutch (2003)[11] and Norwegian (2000)[12] general practice guidelines for the treatment of uncomplicated hypertension there is a stated preference for thiazides as monotherapy. This is comparable to JNC-7, which recommends thiazide

FIGURE 1 - Total utilisation in DDDs/1000 persons/day (A) and relative utilisation in % (B) of antihypertensive agents per country

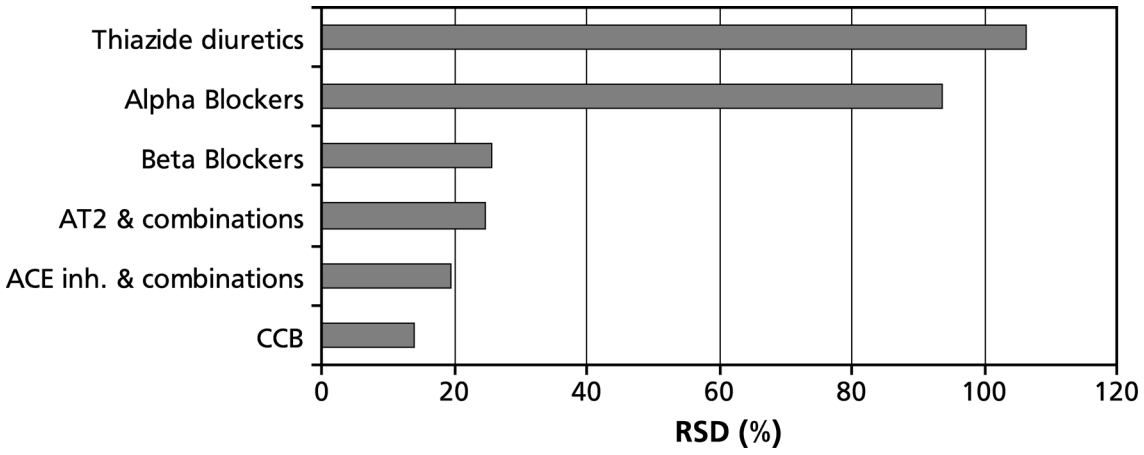


CCB = dihydropyridine calcium antagonists; ACE inh. = ACE-inhibitors; AT2 = angiotensin II inhibitors

diuretics as the first treatment of choice as well.[13] Where guidelines advocated TDs, TD usage was below (Norway) or just above (The Netherlands) median use.

The second group consists of guidelines stating a preference for thiazides, ACE-inhibitors or beta-blockers as a first choice. A previous Danish guideline (1999),[14] the Finnish general practice guideline (2002)[15] and the guideline published by the Drug Committee of the German Medical Association (2004)[16] are examples of this group.

FIGURE 2 - Relative standard deviation (RSD) across countries per drug class



AT2 = angiotensin II inhibitors; ACE inh. = ACE-inhibitors; CCB = dihydropyridine calcium antagonists

A third group of guidelines is in line with the WHO/ISH guideline (1999)[17] and the guideline published by the European Society for Hypertension (2003).[18] In these guidelines either thiazide diuretics, beta-blockers, calcium antagonists, ACE inhibitors or angiotensin II receptor blockers, are suitable first choice drugs in the treatment of uncomplicated hypertension. The 2004 guidelines by Danish Heart Association/Danish Hypertension Society,[19] and the German Hypertension Society [20] belong to this group.

In Sweden, the most recent national guideline was published in 1993 and seems to be outdated in the light of the recent evidence. A few years ago, county level formulary committees were made responsible for drug lists and clinical practice guidelines in Sweden.[21] We did not evaluate these local guidelines. Recently,

The Swedish Council on Technology Assessment in Health Care published a systematic review in which all drug classes were regarded as equally effective.[22]
In none of the guidelines the current utilisation of antihypertensive agents in the respective country was discussed.

DISCUSSION

This study shows large differences in both the relative and absolute utilisation of antihypertensive agents. Furthermore, the relative standard deviation, as depicted in Figure 2, shows that the between-country variation of classes such as thiazide diuretics and alpha-blockers is particularly pronounced. Especially for thiazide diuretics the difference between the six countries is remarkable. Thiazide diuretics are recommended in all included guidelines as a valid first choice, they have a long track record, are cost-effective and are supported by solid evidence.[23] However, they also show the largest variation in use, indicating strong variability in acceptance in clinical practice across the six studied countries. The variation in utilisation for this class remains large even when the use of thiazide diuretics in combination preparations, i.e. together with an angiotensin II receptor blocker or an ACE-inhibitor, is taken into consideration. The high use of alpha-blockers for the treatment of hypertension in Norway has also been described elsewhere.[24]
From a cost perspective, special interest goes out to one of the newest drug classes for the treatment of hypertension: the angiotensin II receptor blockers and their combinations. In this analysis, this class did not show a variation in use distinct from ACE-inhibitors, beta-blockers or calcium antagonists. This suggests comparable market penetration in all six countries.
Part of the absolute differences in utilisation may be explained by dissimilarity in the prevalence of hypertension. A recent survey in people between the ages of 35 and 64 has shown a relatively high prevalence of hypertension in Germany (55.3%) and Finland (48.7%) when compared to Sweden (38.4%), this study used the same measurement method in each country.[5] When adjusted for these figures, nearly all variation in absolute utilisation rates can be explained by differences in hypertension prevalence. For the other countries, no data on hypertension was available, to our knowledge, that compared the prevalence using the same methodology. However, we assume that a major part of absolute

variation in these countries can be explained in this way as well. Furthermore, international differences in dosing and varying undertreatment of hypertension may also be an explanation.[25] Differences in population age and gender compositon of the respective countries were relatively small.[8] For both absolute and relative differences, the various approaches to cope with the challenges of the pharmaceutical marketplace when it comes to price setting, reimbursement restrictions and insurance schemes surely also play a role. For example, the general absence of co-payments in the Netherlands creates little economic disincentives for prescribing more expensive antihypertensive drugs. However, the effects of more graduated reimbursement systems (e.g. depending on total drug use of a patient), as used in Denmark and Sweden in 2003, make the effects hard to ascertain.

In these Northern European countries we did not find guideline preferences to be related to the established prescribing practices. International studies on guideline adherence in other fields of cardiovascular disease, such as coronary heart disease[26] and heart failure[27] show that the discrepancy between guidelines and clinical practice is a common phenomenon. Furthermore, the lack of convergence between international guidelines has also been suggested to play a role.[28,29] Of course, it is not realistic to assume that preferences in hypertension guidelines are directly reflected in drug utilisation, given the nature of the disease, the fact that the majority of patients may not be 'uncomplicated' (although a recent study in an American population estimated this to be about 69% of patients)[30], the various indications of the drugs, and the lag time between guideline publication and clinical uptake. However, guidelines are an important tool to translate research into clinical practice, and guidelines such as the Norwegian, which emphasise mono-therapy with a drug hardly popular in day-to-day practice, may find the obstacles posed by established prescribing patterns especially large. Furthermore, none of the guidelines addresses the current utilisation pattern of antihypertensive agents in its target country. The evaluation of existing prescribing habits in guidelines can be an important aid for setting goals and for connecting to current clinical practice.

A limitation of this analysis is the assumption that the major indication for prescribing the studied drugs in all these countries was hypertension, which we believe is true for the Netherlands and Sweden (where a survey of the prescribing of antihypertensives for the indication hypertension corresponds well

with our aggregate utilisation data)[22]. However, this is an assumption for all other studied countries. Alpha-blockers are especially susceptible to misclassification in this study, since their use in the treatment of benign prostatic hyperplasia is sometimes clustered under the same ATC-code. Furthermore, since the indication of prescribing is unknown, it is impossible to judge guideline adherence at the patient level with these findings. We were also not able to study the influences of co-morbidities.

The data were extracted from various sources (wholesaler/dispensing/ reimbursement). However, in this study, our main focus was on the relative use of antihypertensive agents of the different drug classes. We have no reason to believe that selective misclassification of antihypertensive utilisation in a country with regards to drug class plays a significant role. For both countries where reimbursement data was used (The Netherlands, Germany), insurance coverage was extensive. Therefore, we believe that in these countries all data sources give a reasonably complete and comparable estimate of drug consumption in the population, making bias introduced by the different sources of the data small.

Finally, the RSD measure used here may have a tendency to overemphasise the variation when relative utilisation as a percentage of total utilisation is small. However, large differences remain when these limitations are taken into account. The between-country variation in this study is substantial, and should form the basis for further discussion.

In conclusion, utilisation patterns of antihypertensive agents vary largely across the six countries studied, both in absolute and relative terms. In this study, the relative standard deviation proved to be a practically feasible and useful tool to study variation in drug utilisation between countries. Although thiazide diuretics are included in all guidelines and have a proven record, the absolute level of use was low and the between-country variability in utilisation high. Thiazide diuretics share this high variability with alpha-blockers, of which the effectiveness is disputed. Furthermore, none of the guidelines discussed current utilisation, and in some studied countries guidelines seem disconnected from drug use in clinical practice. Whether this reflects a need for a change in prescribing or a re-evaluation of guidelines warrants further research.

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chapter 3.4

chapter 3.4

Seige-cycles as a learning device in pharmacovigilance

This manuscript is based on two case studies that were conducted in the context of the Frauenhofer report 'Assessment of the European Community System of Pharmacovigilance', 2005 that was commissioned by the European Commission (DG Enterprise and Industry)

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ABSTRACT

The Seige cycle is a general abstraction of drug careers. The Seige cycle facilitates a comparative long-term perspective on the development, use and governance of various agents or classes of agents. In this study we propose the use of a Seige cycle model to study two drug safety cases: the market withdrawal of cerivastatin (Lipobay®) and the discussion about the relationship between Selective Serotonin Re-uptake Inhibitors (SSRIs) and suicide.

For both cases we describe the regulatory landscape in which the drug emerges at the moment of market authorisation, followed by the transactions between key actors that changed the regulatory landscape, and, using publication counts, we show how the debate in the scientific literature evolved. Finally, we superimpose these dynamics on the Seige-cycle. Both cases show strong variation in the roles of the key actors in the development of the safety case. Furthermore, both cases show different dynamics over time and can be placed at different points on the Seige-cycle.

In conclusion, the Seige-cycle framework used in this study could be a useful tool to study drug safety issues in a life-cycle related context. Future studies should develop this method further and should look at ways to quantify Seige-cycle.

INTRODUCTION

When clinical practice and the general public are exposed to a drug safety question, a range of medical, regulatory, scientific, and societal responses will arise. In principle, decisions by regulators are based on the weighing of the 'needs' for a drug versus the 'concerns' about the adverse effects of a drug in light of the available evidence, expressed as a Benefit-Risk (B/R) assessment. These responses can be studied from various perspectives that each take into account particular factors. For example, when drug regulatory authorities are studied from a political science perspective, models for predicting the outcome of the decision process include the reputation of the institution, the credibility of the manufacturer or the influence of patients and patient organisations.[1]

However, the social dynamics of drug use and innovation are often missing from such discussions. Medicines have challenging, and sometimes complex, life-cycles, with diverse actors, social systems, and institutions determining the balance between perceived benefits, needs and concerns. Pieters and Snelders have shown in previous studies that, despite the fact that these life-cycles evolve and mutate with social and technological change, they share a common pattern, the so-called Seige-cycle.[2-4] In this study we want to focus on the (inter)relationships between these Seige-cycles and the initial regulatory response to drug-induced safety issue. We will illustrate the usefulness of the analytical framework of Seige-cycles with two safety cases: the market withdrawal of the lipid-lowering drug cerivastatin (Lipobay®) in 2001, and the controversy over the increased risk of suicide in children during treatment with antidepressants belonging to the class of Selective Serotonin Reuptake Inhibitors (SSRIs) (2003 onward). We will discuss how a dynamic life-cycle perspective for medicinal products can be useful for future pharmacovigilance planning and thinking.

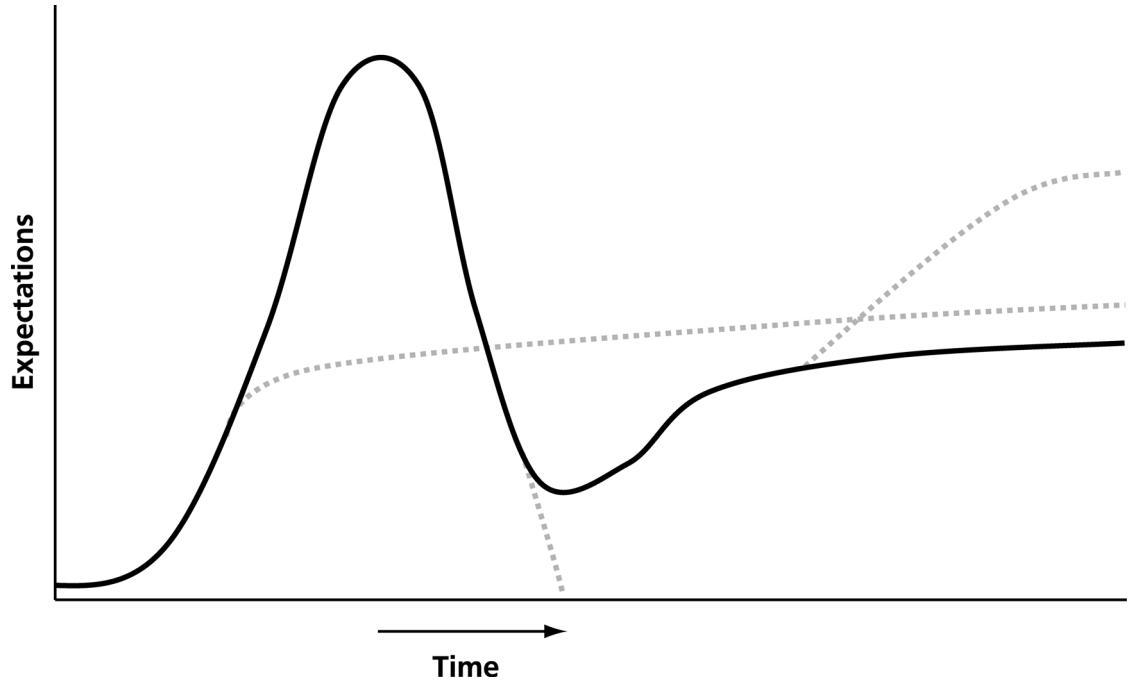
THEORETICAL FRAMEWORK – THE SEIGE-CYCLE AS PART OF A LIFE-CYCLE APPROACH

The idea of a cyclical dynamic of the careers of (psychotropic) medicines, is not a new concept. In 1912 the German psychiatrist Max Seige already spoke about common oscillations in the development and use of sedatives and hypnotics:

"The first reports sounded in every respect extremely favourable; but before long it became clear that [these drugs] did not satisfy the traditional conditions of cito, tuto et jucunde [quickly, safely, and pleasantly], at least, that they already in small doses caused all kinds of unpleasant or detrimental side-effects. Finally most of them found a small limited special territory, in which the conscientious physician uses them."[5]

Following Seige, a number of researchers have pointed at a shared cyclical course of the careers of psychotropics and other kinds of drugs.[6-9] Despite their fundamental differences, medicinal products appear to go through relatively predictable waves of initial popularity, usually enthusiasm, then resistance-rejection, and finally a more balanced appraisal (Figure 1). With variations in durations, intensities and other dimensions this Seige-cycle pattern has been shown to hold extremely well for almost every single class of psychotropics.[10,11] A comparable model has also been proposed by Gartner et al. for information technology.[12]

FIGURE 1 - A typical Seige cycle for pharmaceuticals



A typical Seige cycle (black solid line) showing initial popularity, followed by resistance/rejection, and finally a more balanced appraisal. Dashed lines indicate alternative patterns.

The Seige-cycle is not intended to be viewed as a 'universal' law, but as an analytical tool, a learning device. As a general abstraction of the dynamics of a drug career, the Seige-cycle facilitates a comparative long-term perspective on the development, use and regulation of various medicinal products or classes of agents. Each step or stage in the life-cycle may be conceived as a mini-system with its own dynamics. This involves a specific context, a group of key actors, and various transactions among these actors as part of the changing regulatory landscape.[13] Careers of medicinal products or life-cycles mutate, adapt and respond to social, regulatory, economic and technological events.

Given the dynamic activity at any point in time, it is not surprising that different trajectories may emerge: the careers of medicinal products involve bifurcations, jumps, improvisations, impasses and dead-ends. These may result from difficulties in clinical trials, new indications, changing marketing practices, public attitudes or drug policies. These more or less predictable events at one or another stage are likely to influence the nature and course of the cycle.

METHODS

To explore the applicability of the Seige-cycle in different settings, we have chosen two distinctive safety cases. The first case focuses on the lipid-lowering drug cerivastatin, which was withdrawn from the market on 8 August 2001 because of an increased risk of rhabdomyolysis (a potentially lethal adverse effect with at that time a relatively unknown mechanism) particularly if used in combination with gemfibrozil from another lipid lowering drug class, a fibrate.[14]

The second case is the possible association between the use of SSRIs and an increased suicide risk (especially in children). The potential association between SSRIs and suicide has always been a multi-faceted one. On the one hand, since depression itself is a primary risk for suicide, studies at both the controlled trial and the population observational level have revealed an association between SSRI use and a *de*crease in suicide risk.[15] On the other hand, suicide as an *adverse effect* has been reported from early on for SSRIs.[16]

Each of the cases is sketched below by taking into account a same set of key actors which operate in the pharmaceutical regulatory landscape. These key actors are patients and patient organisations, health professionals, companies,

academia, government regulators, the media, lobby and pressure groups and politicians. First, we will describe the regulatory landscape in which the case medicinal product emerged at the moment of market authorisation. Secondly, we will describe how the transactions between the key actors changed the regulatory landscape and the careers of case products under survey. Thirdly we will superimpose these dynamics on the Seige-cycle.

CASE 1 – WITHDRAWAL OF CERIVASTATIN (LIPOBAY®, BAYCOL®)

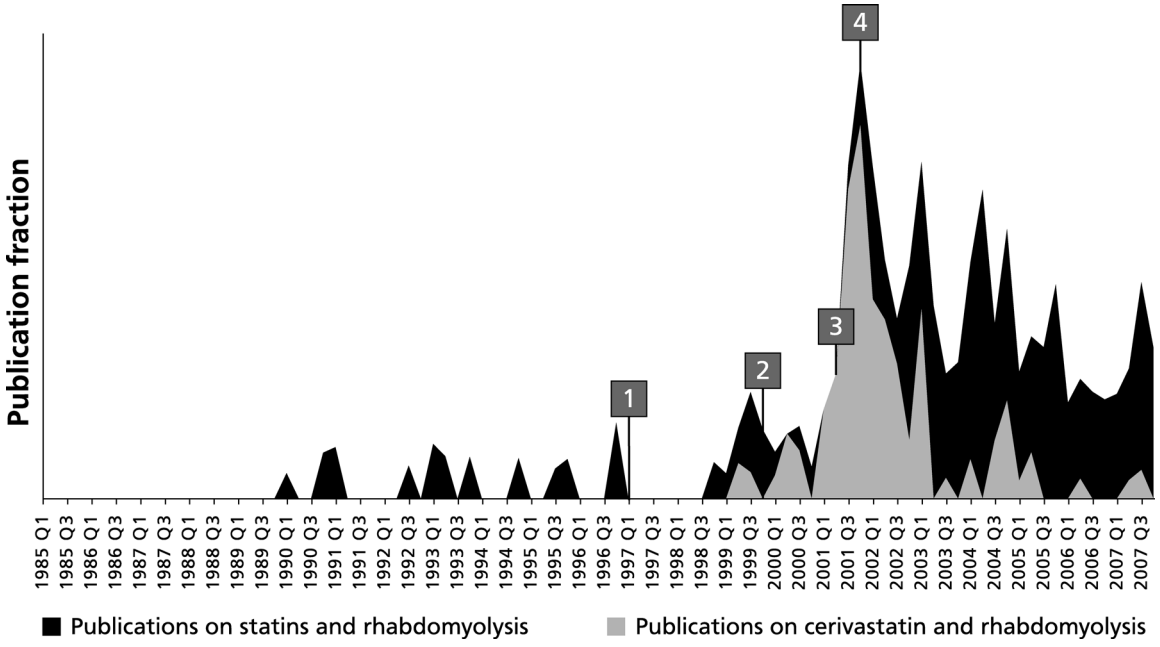
Initial landscape at market authorisation

The first statin, lovastatin, entered the market in 1987, quickly followed by simvastatin in 1988. Initially, the adoption of statins in clinical practice was slow because the effects of lowering cholesterol on cardiovascular mortality were still under discussion. In 1994 the publication of the Scandinavian Simvastatin Survival Study (4S) proved to be a critical turning point. This study showed strong reductions in all-cause and cardiovascular mortality in patients with ischemic heart disease.[17] In the next two years, studies were published that extended the evidence for effectiveness of statins by reducing cardiovascular mortality to primary prevention in patients with hypercholesterolemia.[18,19] This meant that the initial phase of the statin Seige-cycle was extensive, but the expectations about the whole class of statins as an effective treatment were clearly higher than ever.

At market authorisation (1997), with several competing compounds already in clinical use, cerivastatin was positioned by the producer (Bayer) as a highly potent statin with a low risk for interactions.[20] For example, in a special supplement of the American Journal of Cardiology, the editorial stated that: "Cerivastatin is not only effective and well tolerated in the treatment of a range of dyslipidemias, it also possesses a number of features that distinguish it from other statins, including: 1) high pharmacologic potency, which translates into efficacy at ultra-low doses (0.1–0.3 mg/day); 2) an uncomplicated pharmacokinetic profile; and 3) virtually no interactions with common concomitantly administered drug".[21] Furthermore, cerivastatin was also marketed as being cheaper on a potency basis when compared to competitor drugs, as well as being of synthetic origin (while other statins were 'fungally derived'). [22,23]

The risk of rhabdomyolysis with statins was well known at the moment cerivastatin entered the market. A warning for rhabdomyolysis, including warnings about the interaction with gemfibrozil, was included in the initial cerivastatin product information in the European Union (EU) and in the United States of America (USA) based on discussions between the regulatory communities and the company.[24,25] However, no explicit contraindication for co-prescribing cerivastatin with gemfibrozil was included in the European Summary of Product Characteristics (SmPC).[26]

FIGURE 2 - PUBMED publication fractions for statins + rhabdomyolysis and cerivastatin + rhabdomyolysis (key events are indicated by numbers)



1. Cerivastatin marketed in the EU;
2. A contraindication for the concomitant use of cerivastatin and gemfibrozil is introduced in the USA;
3. Increase in spontaneous reports on rhabdomyolysis with cerivastatin noted in the USA and the EU;
4. Market withdrawal of cerivastatin.

Transactions

An overview of the key transactions from market authorisation, leading up to the withdrawal of cerivastatin is shown in Appendix 1. Figure 2 shows the fraction of PUBMED publications for rhabdomyolysis + statins and rhabdomyolysis +

cerivastatin and a selection of the major events surrounding the safety case. The publications are recorded for 1985-2007, the search was based on MESH terms.[a]
As the figure shows, rhabdomyolysis was not a widely discussed topic in the scientific literature at market authorisation. The first major reports about possible safety concerns related to cerivastatin started to emerge in 1999. In May of that year, Bayer applied for a label change, specifically contraindicating the concomitant use of cerivastatin and gemfibrozil, in the USA market. This was granted in December of 1999. However, at the same time, Bayer was aiming for the marketing of a higher dose statin of 0.8 mg. This dosage form was marketed in the USA in July 2000 and in the UK in March of 2001.
Over its lifetime, the market share of cerivastatin remained small. In 2000, cerivastatin had the smallest share of the statin market in most European countries and the USA where the market share was slightly less than 4% at market withdrawal.[27,28]

Discussion

As the overview (Appendix 1) shows, in 1999 and 2000 the landscape was mainly shaped by transactions between the manufacturer and the regulatory communities. In these interactions, two parallel, but almost contra-acting, tracks can be discerned. For example, on the one hand Bayer aimed to market a new 0.8 mg dose, while at the same time the first reports of an increased risk for rhabdomyoloysis arose and label restrictions were added (e.g. in the USA at the end of 1999). Post-withdrawal analyses and court cases showed extensive internal discussion about the safety of the drug within the company, while the higher 0.8 mg dose of the drug was being marketed.[29,30] The issue of drug potency was obviously perceived as a key factor given the very competitive market place of statins. However, the potency claims for cerivastatin were not substantiated in later clinical evaluations. When the marketed tablet sizes were compared with regard to LDL, HDL and triglyceride changes, cerivastatin was actually one of the least potent statins.[31]
An interesting feature of the case is the diversity in activities of the regulatory communities. While both European and USA regulators were heavily involved

[a] PUBMED search terms: Statins and rhabdomyolysis = ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] AND "Rhabdomyolysis"[Mesh]); cerivastatin and rhabdomyolysis = (cerivastatin [Substance Name] AND "Rhabdomyolysis"[Mesh])

in the case, the USA Food and Drug Administration (FDA) mainly drove the dynamics leading up to the market withdrawal. The EU regulator was in a more reactive role. This was exemplified by the close contact between the FDA and Bayer when the decision to withdraw the drug from the market was made.[32]

With regard to the Seige-cycle, a classical pattern can be discerned in this safety case of cerivastatin. Notwithstanding the attempts by Bayer to market cerivastatin as a highly potent, effective drug, results from studies published after market authorisation led to a strong decrease in the expectations about the drug.[33,34] Furthermore, there were many substitution options for cerivastatin (i.e. other statins that could be used for the same indication) over which cerivastatin had no unique competitive advantage. In this environment, the possibilities for therapeutic substitution heavily influenced the debate about 'needs' versus 'concerns' within the regulatory communities, leading to the drug being vulnerable to strong regulatory intervention.

The cerivastatin case also had an influence on the life-cycle of the statin class as a whole. Although rhabdomyolysis was known at the moment of market authorisation of cerivastatin, the topic only gained real prominence in the scientific literature after the first reports of rhabdomyolysis and cerivastatin were published. After the market withdrawal of cerivastatin, the issue of rhabdomyolysis remained an important issue in the literature, signifying a change in the perception of, and expectations about, statins as a group as well.[17] Especially for newly introduced statins, rhabdomyolysis has continued to be a source of concern. This is exemplified by the discussion about the safety of rosuvastatin (Crestor®), a statin that was marketed in 2003, which also focused on its myotoxicity.[35,36]

CASE 2 – SSRIs AND SUICIDE RISK

Initial landscape at market authorisation

In the late 1980s one of the first SSRIs, fluoxetine (Prozac®), was launched. Prozac was presented as a revolution in the psychopharmacology of depression. Fluoxetine was claimed to selectively restore the serotonine levels in the brain back to normal. By prescribing a compound like fluoxetine that lacked the adverse effects of the older tricyclic antidepressants (TCAs) and MAO-inhibitors,

such as toxicity in overdosing, doctors would be able to provide their patients with a safe and effective antidepression therapy.[37,38]

As is widely known, the message of a revolution in brain chemistry and a therapeutic break-through was picked up rather swiftly. The cycle of events following the introduction of Prozac even took Lilly's marketeers by surprise. In celebrating Prozac as a wonder drug that effects miraculous changes in personality Peter Kramer's 'Listening to Prozac' helped to created a hype that promoted Prozac and other SSRIs like Paxil and Zoloft to the commercially attractive league of blockbusters.[39] In 1994 Prozac was the second best selling drug worldwide, just behind the ulcer drug ranitidine (Zantac®). By the late 1990s and early 2000s the patents of most SSRIs expired, although this did not affect the consumption figures.

In the meantime, depression prevalence rates also continued to rise irresistibly. Within two decades the percentage of the population having depression that requires treatment has risen five fold on average. Depression has developed into the fourth leading contributing factor to the worldwide disease burden.[40]

Over the years, the indication-range of the SSRIs has widened to other conditions such as generalised anxiety disorder, obsessive-compulsive disorder and social phobia as well. At the time that this safety emerged, SSRIs were not authorised EU-wide for the treatment of depression in children, although some drugs in this class were licensed for juvenile treatment of Obsessive Compulsive Disorder or Attention Deficit/Hyperactivity Disorder.[41]

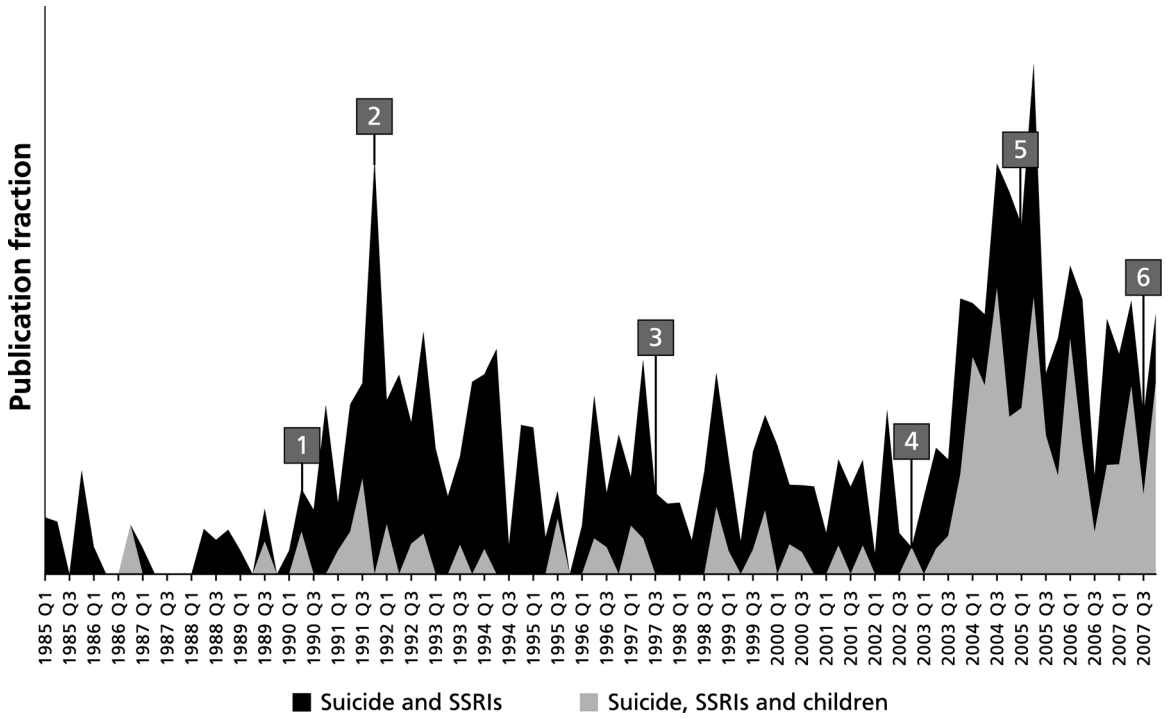
Transactions

The key transactions that have shaped the regulatory landscape for the discussion about the relationship between SSRIs and suicide are shown in Appendix 2. Figure 3 shows the fraction of PUBMED publications on suicide + SSRIs in as well as for suicide + SSRIs in children and some of the major events surrounding the safety case. The publications are recorded for 1985-2007, the search was based on Mesh terms.[b]

When the key transactions are seen against the background of the publications in the scientific literature (Figure 3), four phases in the discussion surrounding the

[b] SSRIs and suicide = (Serotonin Uptake Inhibitors [Pharmacological Action] AND "Suicide"[Mesh]); SSRIs and suicide in children = (Serotonin Uptake Inhibitors [Pharmacological Action] AND "Suicide"[Mesh] AND ("Adolescent"[Mesh] OR "Child"[Mesh]))

FIGURE 3 - PUBMED publication fractions for SSRIs + suicide and SSRIs + suicide + children (key events are indicated by numbers)



1. Publication of first report of suicidal intentions associated with the use of fluoxetine;
2. FDA hearings on the link between SSRI use and suicidality;
3. First randomised trial of an SSRI (fluoxetine) in children;
4. GSK submits new clinical data on paroxetine use in children to regulators/BBC airs 'The secrets of Seroxat';
5. The Committee for Medicinal Products for Human Use (CHMP) recommends a strong warning on suicidality and SSRIs in children;
6. FDA proposes an updated black-box warning.

relationship between SSRIs and suicide can be discerned. The first phase starts with the marketing of the SSRIs in the late 1980s and ends with the FDA advisory committee hearings at the end of 1991, during this phase the debate mainly focused on suicide in adults. The second phase, which saw the topic recede somewhat to the background, starts in 1992 and ends in 2002. In the third phase the issue comes again to the forefront because of the request of one of the companies marketing an SSRI (GlaxoSmithKline [GSK]) for an extended indication for SSRIs to be used in the treatment of depression in children,[42] and the extensive media exposure. This third phase is characterised by heavy activities by regulators, focusing on the relationship between SSRIs and suicide in

children, and ends with the recommendation for a strong warning by EU regulators in April 2005. In the aftermath of these regulatory interventions, discussions are still ongoing.

Discussion

This case shows a very intriguing pattern where an extensive safety discussion was precipitated by an activity of one of the companies marketing an SSRI, i.e. a search for treatment indications for SSRIs in children by GSK, likely in response to USA legislation to stimulate the development of drugs to be used in children and adolescents. This is one of the first instances where regulatory response in a safety case was so heavily driven by the results from unpublished clinical studies submitted by a company. In the follow-up, access to the clinical studies on the effectiveness and safety of paroxetine in children precipitated regulatory action for the whole class of antidepressant drugs.

Because of the long period that this topic has been under discussion, it is not surprising that a wide variety of stakeholders have been involved in shaping the debate over the years. In the first phase, academic research and regulators drove the discussion. The second phase mainly saw the debate move to the scientific arena with little involvement of the regulators. However, this was also a period during which the discussion mostly moved out of the spotlight of the public domain and the media. In the third phase, a combination of media activity and activity by the manufacturer again brought the possible relationship between SSRIs and suicide to the forefront. During this phase there was again heavy intervention by regulators. The fourth phase is characterised by the ongoing discussion about the risks of suicide and SSRI use in children. This involved the same key actors as the third phase, but who are now looking how the benefits and risks of SSRIs can best be balanced in the light of new knowledge.

A specific feature of the SSRI case has been the very important role that was, and is being, played by the media. In the UK, for instance, a BBC documentary and the ensuing media exposure played a key role in driving the public debate and subsequent regulatory responses. With regard to the scientific evidence, it is interesting to note that the initial discussion in the early 1990s focused on suicide in adults, while later, suicide in children was the main issue for discussion.

The role of one of the manufacturers of SSRIs, GSK, has been the subject of much discussion. In a 2004 article it was alleged that internal documents of GSK

showed that the dissemination of trial data was managed "to minimise any negative commercial impact", to cite the words of the Central Medical Affairs team of the company.[43] Furthermore, there was a significant impact of unpublished studies. A meta-analysis of both published and unpublished randomised controlled trials concluded that the influence of unpublished randomised trials was significant. For some drugs, e.g. paroxetine and sertraline, the benefit-risk balance was tipped towards the negative side in childhood depression by including the unpublished data in the meta-analysis.[44] Moreover, in a review in the *British Medical Journal* of methods used in trials of antidepressants in children, the authors concluded that researchers tend to overstate the effectiveness of antidepressants, while deflating the safety risks.[45]

This case again shows the importance of the transactions between the various key actors in shaping the life-cycle of the SSRI class. One could argue that the early discussion about the risk of SSRIs took place during the initial phase of market uptake during which the benefit-risk assessment for SSRIs was still underway. During the following period, SSRIs were firmly established as an effective treatment for depression. This was also a period with few transactions between key actors that influenced the regulatory landscape for the drug. In recent years, however, discussions about the effectiveness and safety of SSRIs have re-emerged, also influencing the expectations about the whole drug class.[46] Against this background, the discussion about the relationship between SSRIs and suicide took place.

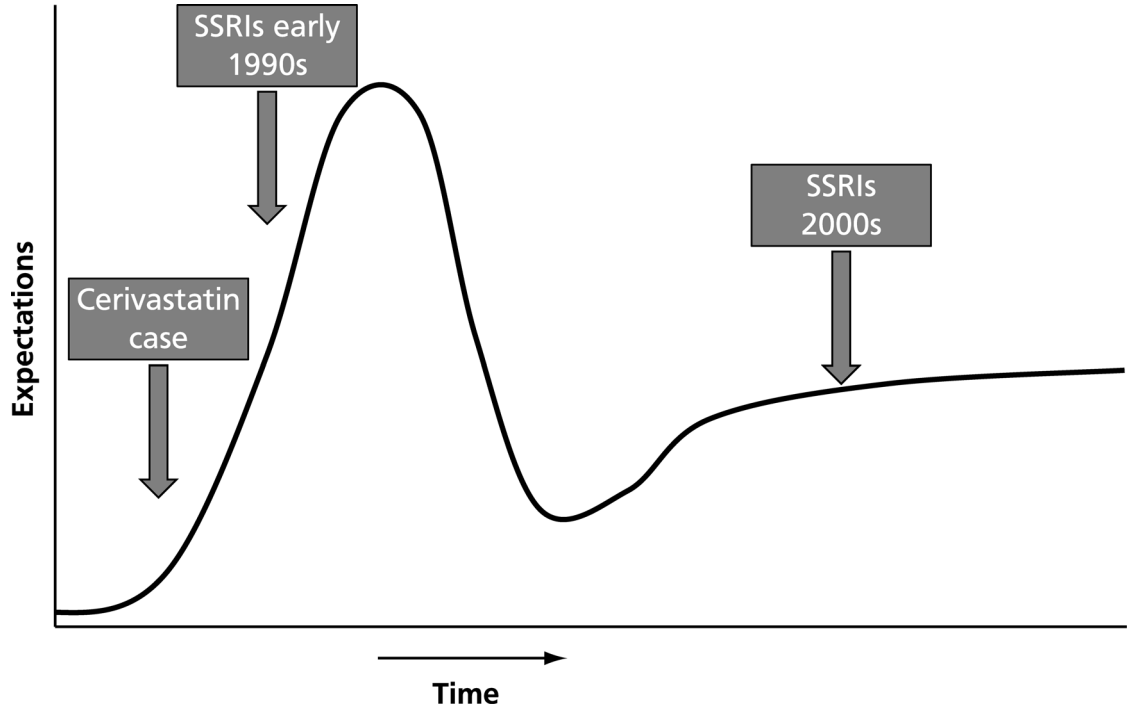
This case also shows how regulatory incentives to stimulate pharmaceutical research, e.g. the paediatric 6 months exclusivity provisions in the USA, have played a catalysing role in the discussion. This particular incentive has led to many drug studies being performed in children,[47] and has played a major role in GSK submitting initial clinical information on the safety case to the FDA.

GENERAL DISCUSSION & CONCLUSIONS

In this study we explored the changing regulatory landscape for two safety cases. We found that in the two cases the role of the key actors in driving the life-cycle varied dramatically over time. In the first case, changes in the landscape were mainly driven by the interactions between the market authorisation holder and

the regulator. In contrast, the second case showed a complex mix between companies, lay media, and regulators as the most important drivers.

FIGURE 4 - A typical Seige cycle with position of the cerivastatin case, the first discussion about SSRIs and suicide in the early 1990s, and the discussion in the 2000s marked on the conceptual cycle



In both cases we found pertinent characteristic features of the Seige-cycle. The cerivastatin case mainly highlights the problems drugs can encounter in the early phases of market uptake especially when there is a disconnect between the expectations of the company and the medical communities in the context of other drugs in the same class. The SSRI case shows that the discussion about certain adverse events (in this case suicide) can have a cyclical pattern. This case also provides preliminary evidence that such discussion can be especially prominent in the early phase of the life-cycle of in, this case, a drug class, can disappear from the radar for quite some time before re-emerging in full intensity years later during the later stages of the drug life-cycle. In Figure 4 we have attempted to place the two safety cases on the life-cycle with the cerivastatin case

taking place early in the post-marketing life-cycle and the SSRI case in both the early and the late phase of the life-cycle.

TABLE 1 – Important features of the two drug safety cases

	SSRIs AND SUICIDE IN CHILDREN (2003-2005)	CERIVASTATIN AND RHABDOMYOLYSIS (2001)
DRUG/ADVERSE FFECT		
Concerned drug(s)	Whole drug class, marketed since late 1980s/early1990s	Cerivastatin introduced in 1997, class marketed in 1980s
Utilisation	Large drug class with high market impact	Large drug class with high market impact
Type of event	Suicidal ideation / suicide	Rhabdomyolysis
Prevalence	Rare adverse event	Rare Adverse event
Dose dependent	No information available	Yes (related to LDL-lowering)
Mechanism	Unknown	Unknown
Class effect?	Yes probably, differences in size of effect between drugs?	Yes, but large differences between drugs
PATIENT POPULATION		
Concerned population	Children (<18 years)	Adults
Event	Rare in population, but associated with indication	Rare in population not associated with indication
Type of drug use	Off-label (little evidence)	Labelled use (evidence of efficacy widely available)
REGULATORY		
Prime data source	Clinical trial data	Observational research/ spontaneous reporting
Role of EMEA	EMEA deeply involved in debate	FDA and MAH in hot seat / EMEA in a more 'reactive' role
Regulatory outcome in EU	Safety restrictions on whole drug class	Market withdrawal of single drug
Role of observational research	Supportive/confirmatory role in relation to clinical data	Primary driver in regulatory response

EMEA = European Medicines Agency; FDA = Food and Drug Administration; MAH = Market Authorisation Holder

The two cases, however, differ on a number of technical aspects, which are shown in Table 1. The first case, cerivastatin, focuses on a single drug while the SSRI case relates to a whole drug class. Furthermore, the association between the

adverse effect and the therapeutic indication also differs, while it is closely linked to the major indication (depression) in SSRIs, this is not the case for cerivastatin. Another important feature of the safety case was the source of the scientific evidence that played a determining role in the debate. In the SSRI case, evidence from randomised trials conducted in a clinical research setting was the driver in the regulatory process. In contrast, spontaneous adverse event reports from clinical practice led to the market withdrawal in the end of cerivastatin. These differences should be taken into consideration when interpreting this case.

For sure, analyses as presented here always carry the risk of being a selective snapshot of the course of events, an oversimplification or a personal, possibly biased, picture of reality. We believe, however, that using an approach in which the changing regulatory landscape for a drug is interpreted as activities by key actors that impact on a Seige-cycle can be of added value when studying drug safety cases, if conducted in a careful fashion and considering all its limitations. This type of analysis may add a historical perspective to a safety case, and provides a framework to map the role of different actors.

This study also has some other limitations that should be considered. It is very difficult to measure the Seige-cycle directly. In this study we used a method of counting the number of publications in PUBMED as a surrogate marker for measuring the development of the debate surrounding safety issues. This method is not always particularly specific. For example, publications on SSRIs and suicide may also relate to attempted suicides with these drugs. However, notwithstanding this limitation, we believe that the method presented here is useful for getting a general overview of the topic. Of course, it would be desirable to measure the 'expectations' about a drug or drug class directly. This could be done by, for example, carefully analysing publications in professional journals, newspapers or trade journals. This data could be complemented with information about drug sales or other markers of use in clinical practice.

In conclusion, there are lessons to be learned in looking across historical safety cases for shaping the future of pharmacovigilance. There is a constant need for learning, knowing that most actors are constantly under great time pressure to act and make decisions in the absence of a full picture of all the facts. This paper shows how scientific, regulatory and societal issues come together when 'things go wrong'. The analysis also emphasises that there is no single prevailing truth or perspective in unravelling such cases. As many in the pharmacovigilance

community are very often actor, scientist and analyst at the same moment, we carry the responsibility to be transparent, open-minded and constructive in finding the right nuance. The Seige-cycle framework used in this study could be a useful learning device in this context. By looking at drug safety issues as driven by transactions between key actors that modify a regulatory landscape, new insights into how and why some safety issues lead to regulatory interventions at a certain moment in time and others do not can be gained. Future studies should develop this method in more detail and should look at ways to further quantify Seige-cycle.

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APPENDIX 1 – KEY EVENTS IN THE CERIVASTATIN CASE

February 1997	Cerivastatin (Lipobay®) is marketed in the EU.
May 1999	Based on spontaneous reports for rhabdomyolysis in patients using cerivastatinwith a fibrate, Bayer requests a label change for the FDA label.
December 1999	At the request of Bayer, a contraindication for the concomitant use of cerivastatin and gemfibrozil is added to the USA drug label.
July 2000	The FDA approves a new 0.8 mg dose of cerivastatin, the highest yet.
March 2001	A 0.8 mg dose of cerivastatin is marketed in the UK.
Spring of 2001	The FDA noted an increase in spontaneous reports related to cerivastatin and contacted Bayer.[A] At the same in the EU, based on a Periodic Safety Update Report (PSUR) submitted to the UK Medicines Control Agency, additional information from the Market Authorisation Holder (MAH) about the safety of cerivastatin is requested.
30 May 2001	The Spanish pharmacovigilance system reports 34 cases of rhabdomyolysis associated with cerivastatin.[B] In 65% of these cases the patient had been on concomitant treatment with the gemfibrozil. Other EU countries did not report an increased risk. A class review of all HMG-CoA-reductase inhibitors at the level of the EMEA Pharmacovigilance Working Party (PhVWP) was proposed by Spain.
19 June 2001	The UK circulates a Rapid Alert with the proposal to contraindicate the concurrent use of cerivastatin and gemfibrozil.
26 June 2001	An Urgent Safety Restriction (USR) is published. The changes to the SmPC included: 1) a new contraindication to the concomitant use of cerivastatin and gemfibrozil; 2) the restriction of the maximum dose to 0.4 mg; and 3) a stronger emphasis on the importance of dose titration.[41]
July 2001	The EMEA PhVWP informed the FDA about the USR, the changes to the SmPC and about the further assessment planned for all statins at the level of the PhVWP. The FDA informed the PhVWP that following the contraindication for coprescribing of gemfibrozil in 1999, the FDA had not seen a decrease of co-prescription of gemfibrozil. The PhVWP decided to further discuss that issue in September and October 2001 meeting.
1 August 2001	Bayer stops marketing its 0.8 mg dose cerivastatin in the USA, the 0.8 mg had already been suspended in the EU. At the same time the FDA asked Bayer to re-evaluate the risk-benefit profile of all marketed doses, based on the reports of 31 deaths in which cerivastatin was implicated.[C]
7 August 2001	The UK authorities suggest that the MAH is considering withdrawal of cerivastatin the following day. The MAH confirmed their intended drug withdrawal at 5:30 p.m. UK time. At about 6:30 p.m. UK time the UK sent a Rapid Alert, informing all member states, the European commission and the EMEA of the MAH's intention to voluntarily withdraw cerivastatin from all markets world-wide.
8 August 2001	Cerivastatin is withdrawn from the market.

EU = European Union; FDA = Food and Drug Administration; UK = United Kingdom; MAH = Market Authorisation Holder; HMG-CoA = 3-hydroxy-3-methylglutaryl-Coenzyme A; PhVWP = Pharmacovigilance Working Party; EMEA = European Medicines Agency

(*legend Appendix 1 continued*)

A) Marwick C. Bayer is forced to release documents over withdrawal of cerivastatin. BMJ 2003;326:518.
B) Subdirector general de seguridad de medicamentos. Notas de la agencia española del medicamento, nota informativa, comunicación sobre riesgos de medicamentos, ref: 2001/03, 30 de mayo de 2001, cerivastatina y casos de rabdomiolisis. Available from: http://www.sefh.es/alertas/alertaceri.htm (Accessed 14 June 2008).
C) Mosely J. Risk management: A European regulatory perspective. Drug Saf 2004;27:499-508.

APPENDIX 2 – KEY EVENTS IN THE SSRI CASE

February 1990	Teicher et al. publish the first report of suicidal intentions associated with the use of fluoxetine.[A]
March 1991	First publication of on self-destructive phenomena in children and adolescents during fluoxetine treatment.[B]
September 1991	The Psychopharmacological Advisory Committee of the FDA advises that there is no causative link between using an SSRI and suicidality.[C]
November 1997	Publication of the first randomised trial of a SSRI (fluoxetine) in children.[D]
2002	GSK applies for a 6-month market exclusivity extension with the FDA based on pediatric clinical data.
October 2002	BBC airs an episode of Panorama entitled 'The secrets of Seroxat'.[E] The UK Medicines and Healthcare products Regulatory Agency (MHRA) meets with GSK to discuss the safety of paroxetine.
February 2003	GSK submits an update of the clinical trial data on suicidal behavior to the MHRA, this was not prompted by a request from the MHRA.
April 2003	The MHRA creates an Expert Working Group to review the safety of SSRIs, with particular reference to suicidal behaviour.
May 2003	GSK submits additional work on the safety of paroxetine to the MHRA and the FDA.
June 2003	Warning on the use of paroxetine in children by the UK CSM and the FDA. Start of a European referral procedure.
October 2003	The FDA releases a public health advisory calling attention to reports of the occurrence of suicidality in clinical trials for various antidepressant drugs in pediatric patients with major depressive disorder.
December 2003	UK review of SSRIs in children finalised. Only fluoxetine has a positive risk benefit profile.
March 2004	FDA releases a public health advisory asking manufacturers of SSRIs to include in their labeling "a warning statement that recommends close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality."
April 2004	CPMP finalises an EU referral procedure: the balance for paroxetine remained positive in adults, but "the drug should not be used in children and adolescents as clinical trials have found paroxetine to be associated with increased risk of suicidal behavior and hostility."

August 2004	Publication of the Treatment for Adlescents with Depression Study (TADS), which demonstrated an elevated risk of suicide-related events in both fluoxetin arms compared to palacebo.[F]
October 2004	The FDA directs manufacturers to include a black box warning "that describes the increased risk of suicidality in children and adolescents given antidepressant medications and notes what uses the drugs have been approved or not approved for in these patient ."
December 2004	The MHRA releases the final results of a review of the safety of SSRIs. The review concludest that "a modest increase in the risk of suicidal thoughts and self-harm for SSRIs compared with placebo cannot be ruled out." However, "There is good evidence from large population studies that there is no clear increase in the risk of suicide from SSRIs compared to other antidepressants." With regard to young adults it was stated that this group "should be closely monitored, as a precautionary measure."
April 2005	The CHMP concludes in a review that suicide related behaviour and hostility were more frequently observed in clinical trials among children and adolescents using SSRIs and SNRIs than in those on placebo. The CHMP recommends a strong warning.
July 2005	The FDA publishes a talk paper in which a review for the risk of suicide in adults is announced.
May 2007	FDA proposes that all manufacturers of antidepressants update black box warnings to "include warnings about increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment.

SSRI = Selective Serotonin Re-uptake Inhibitors; FDA = Food and Drug Administration; GSK = GlaxoSmithKline; UK = United Kingdom; MHRA = Medicines and Healthcare products Regulatory Agency; CSM = Committee on Safety of Medicines; CPMP = Committee for Proprietary Medicinal Products; EU = European Union; CHMP = Committee for Medicinal Products for Human Use; SNRI = Serotonin-Norepinephrine Reuptake Inhibitor

A) Teicher MH, Glod, C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990;147:207-210.
B) King RA, Riddle MA, Chappell PB, Hardin MT, Anderson GM, Lombroso P, et al. Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. J Am Acad Child Adolesc Psychiatry 1991;2:179-186.
C) Warning label on antidepressant is opposed. New York Times (Late Edition). 1991 Sep 21; Sect. 1:22 (col. 1).
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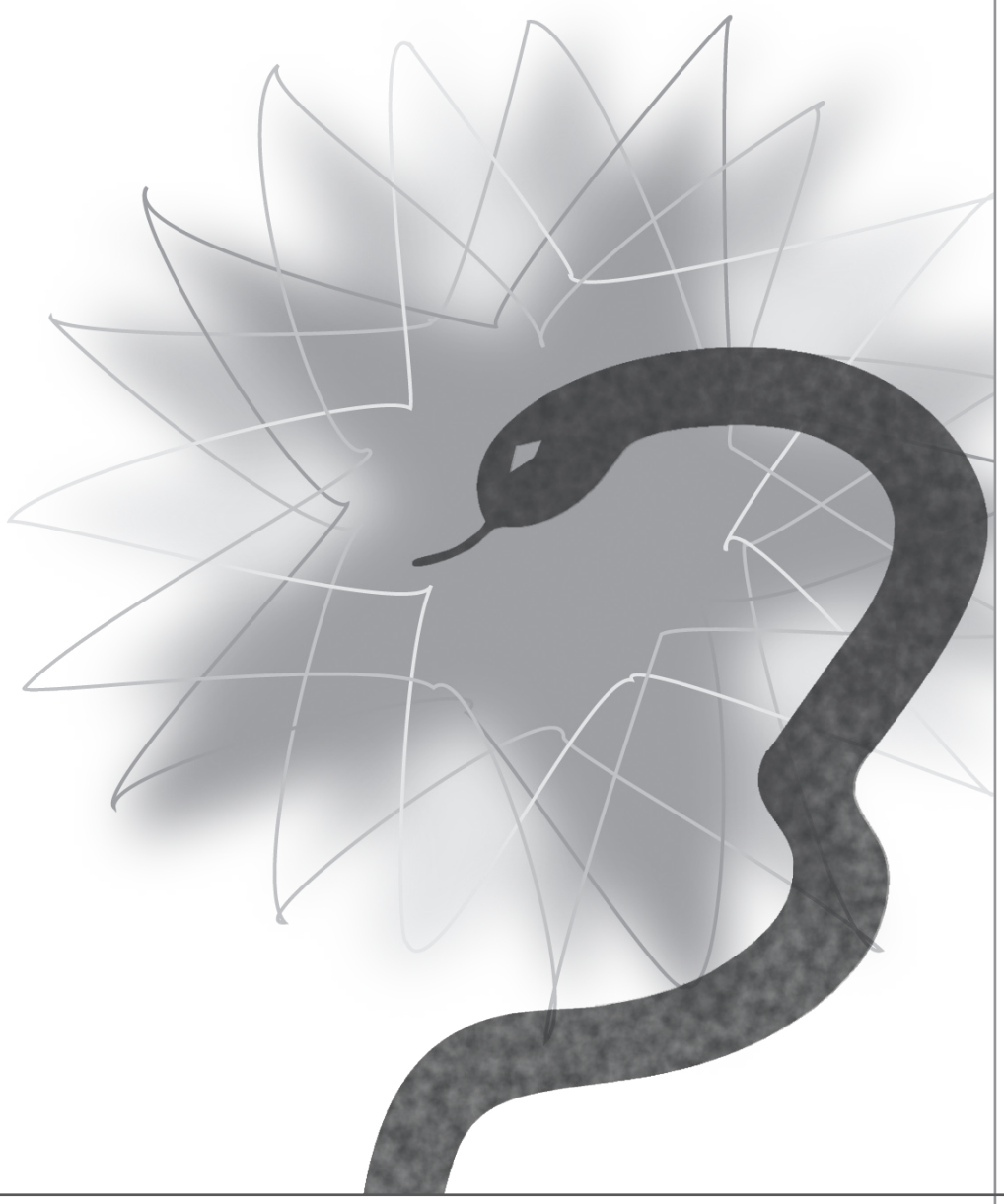
Pharmacoepidemiology as a learning device in pharmaceutical innovation



chapter 4

chapter

chapter 4.1

The association between exposure to COX-2 inhibitors and schizophrenia deterioration: a nested case-control study

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ABSTRACT

Background

Cyclooxygenase-2 (COX-2) inhibitors have been reported to have beneficial effects on schizophrenia. This observational study assesses the association between exposure to COX-2i and/or non-steroidal anti-inflammatory drugs (NSAIDs) and schizophrenia deterioration.

Methods

We conducted a case-control study within a cohort (n=3485) of antipsychotic users with a schizophrenia diagnosis (ICD-9=295.x) in IMS-Lifelink, a US claims database. Case events indicating exacerbation of schizophrenia were: switching antipsychotic medication, starting combination therapy, using parenteral antipsychotics or an increasing dose. For each case one control was selected. Exposure to COX-2 inhibitors/NSAIDs (current/recent/none) and cumulative exposure in Defined Daily Doses 90 days before the index/event date were assessed. Age, sex and co-medication were evaluated as confounders. Logistic regression analysis was used to assess the association.

Results

1443 case events occurred. For current use, no benefit on schizophrenia case events from exposure to COX-2 inhibitors was found (adjusted odds ratio [OR] 1.16; 95% confidence interval [CI] 0.83-1.62). Instead, recent COX-2 inhibitor use with a duration of 0 to 93 days was associated with an increased risk for schizophrenia deterioration (adjusted OR 2.56; 95%CI 1.35-4.87). This association was strongest in rofecoxib. No relation was found for NSAIDs.

Conclusion

The use of COX-2 inhibitors was not associated with a decreased risk for schizophrenia deterioration in this population.

INTRODUCTION

Cyclooxygenase-2 (COX-2) inhibitors were initially marketed for the treatment of pain in osteoarthritis and, in the USA, for acute pain. Research into the effects of this drug class has extended beyond these indications. In recent years several new functions of the different isoforms of the cyclooxygenase enzyme in (patho)physiological processes have been discovered. One of these discoveries is the existence of constitutively expressed cyclooxygenase-2 in the central nervous system. This finding has sparked interest in the potential therapeutic benefits of the selective inhibition of cyclooxygenase-2 in psychiatric illnesses.[1,2] Furthermore, these findings may also lead to a better understanding of the pharmacological basis of psychiatric adverse events that have been reported for non-steroidal anti-inflammatory drugs (NSAIDs).[3]

Recent studies have suggested that COX-2 inhibitors could have a beneficial effect on disease status in patients with schizophrenia when added to regular pharmacological treatment with an antipsychotic.[4] In a small randomised controlled clinical trial (n=50) in patients with an acute exacerbation of schizophrenia, the addition of celecoxib to risperidone improved Positive and Negative Syndrome Scale (PANSS) scores in schizophrenia patients.[5] A more recent trial (n=60) showed a significant superiority of a risperidone and celecoxib combination over risperidone alone in total PANSS scores, treatment of positive symptoms, and general psychopathology symptoms.[6] However, these results were not confirmed in another trial among continuously ill outpatients (n=38).[7]

The objective of this study was to assess the association between exposure to COX-2 inhibitors, NSAIDs, or both and the deterioration of schizophrenia in a daily practice setting.

METHODS

Setting

We conducted a case-control study nested within a cohort of pharmacologically treated patients with schizophrenia, using data from the IMS-Lifelink database. IMS-Lifelink is a US claims database and contains information on health care utilisation of 1.8 million current and former employees and their dependents. The enrolees are situated mostly in the Midwest and on the East Coast of the

United States. The database includes data on claims for prescriptions, hospitalisations, diagnostic/therapeutic procedures, and physician visits. The database covers a period from 1992 to 31 December 2002.

Cohort selection

A study cohort was selected from the Lifelink database. A patient was included in the cohort if a diagnosis of schizophrenia (ICD-9 code 295.X) was recorded anywhere in the diagnosis history after 1992 and if at least three prescriptions were claimed for an oral antipsychotic drug (IMS USC codes 64190 – phenothiazine derivatives - and 64110 – other antipsychotics) after 1 January 2000. The study period ended on 31 December 2002.

The date of the first prescription for an antipsychotic drug after 1 January 2000 marked the start of follow-up; this coincides with the introduction of COX-2 inhibitors. Follow-up ended with either the end of the study period, the date on which a patient left the insurance scheme, or when no prescription for an antipsychotic drug was filled for 180 days, whichever came first. In the latter case, the date of the last prescription was recorded as the end of follow-up.

Patients were not eligible for inclusion in the cohort when information about their coverage by the insurance scheme was lacking from 1 January 1999 onwards, or if patients were not fully covered during the study period. Furthermore, to detect changes in the prescribed daily dose, one of our case events described below, theoretical daily doses were calculated from the prescription records using the number of units dispensed and the number of days for which the drug was supplied according to the pharmacy. Based on this, we also excluded patients with unrealistically high or low calculated daily doses, defined as less than 25% of the smallest tablet size or more than two times the maximum daily dose according to the Food and Drug Administration label or Thomson's Micromedex®.

Case definition

A patient was defined as a case if a medication event occurred during follow-up that we considered being a marker for the deterioration of schizophrenia. We evaluated the following events:

1. Prescription for a parenteral antipsychotic drug;
2. Switching to another antipsychotic: a prescription is dispensed for an antipsychotic with an active substance different from the prior prescription

during the follow-up period. The prior substance does not return in the medication history in the next 180 days;
3. Start of combined use: a prescription for a second antipsychotic substance appears, the substance of the prior antipsychotic prescription returns within the next 180 days after the addition of the second substance;
4. Dose increase: an increase in the calculated daily dose of >30% compared to the previous prescription.

Only the first case event that occurred was taken into account for this analysis, patients were not followed up after the date of this case event. The date of the prescription for the case event was the index date. Furthermore, patients had to be at least 18 years old when the case event occurred. Patients had to use a single antipsychotic (monotherapy) at the start of follow-up. Finally, the medication event should be preceded by a continuous follow-up period of at least 90 days. If the patient did not meet these criteria, the patient was excluded.

Selection of controls

One control was randomly selected for each case using risk-set sampling from all patients in the cohort who had not experienced a case event on the index date. The date on which the case event occurred was the index date for the control. Patients had to be at least 18 years old on the index date to be eligible for selection as a control.

Exposure definition

Exposure to COX-2 inhibitors and (other) NSAIDs before the index date was assessed in two ways. Firstly, we assessed exposure as either 'current', 'recent' or 'none'. A patient was considered a 'current' user when the index date was between the start date of a prescription for an NSAID or a COX-2 inhibitor and the theoretical end date of the prescription, based on the number of days for which the NSAID or COX-2 inhibitor was dispensed according to the pharmacy. 'Recent' users received a last prescription for an NSAID or a COX-2 inhibitor that ended between 1 and 90 days before the index date. All other subjects were classified as 'non exposed'. For 'current' and 'recent' users the relationship between the duration of NSAID or COX-2 inhibitor use and the outcome event was assessed by taking the duration of NSAID or COX-2 inhibitor exposure into account. The duration of exposure was the number of days between the theoretical end date of the last NSAID or COX-2 inhibitor

prescription before the index date and the earliest prior prescription for a NSAID or COX-2 inhibitor without intervening gaps of more than 90 days between the theoretical end date of a COX-2 inhibitor or NSAID prescription and the following prescription. The NSAID or COX-2 inhibitor groups were divided in three duration levels based on tertiles of the COX-2 inhibitor group.
Secondly, we calculated cumulative exposure in the 90 days before the index date as Defined Daily Doses (DDDs), a dosage measure defined by the World Health Organisation. When a DDD was not available, an average daily dose in adults was retrieved from Thomson's Micromedex®. Cases and controls were divided in three exposure levels with regards to DDDs, based on tertiles.

Statistical analysis

A logistic regression model was used to estimate the association between the occurrence of a marker for a change in disease status and the use of COX-2 inhibitors or other NSAIDs. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted for potential confounding by including in the model: age, sex and use of other medications in the past 365 days (antiepileptics, antidepressants, Parkinson's medication or corticosteroids). All analyses were performed with SPSS, version 13 (SPSS Inc, Chicago Ill.).

RESULTS

The Lifelink database contained 10 066 patients with at least one schizophrenia diagnosis after 1 January 1992. Our final cohort of antipsychotic users comprised 3385 patients. After the start of follow-up an event occurred in 1443 patients. Based on the calendar date 1443 controls were sampled from the cohort. A description of cases and controls is given in Table 1. The high prevalence of antiepileptics in the cases and controls is caused by valproic acid, carbamazepine and clonazepam, which are frequently used for psychiatric indications in this population. The median follow up before an event occurred in the cases was 302 days (average: 374 days). Table 2 shows that the most common event was a dose increase (49.4%), the use of parenteral antipsychotics was least common (2.3%).
When we assessed the relationship between COX-2 inhibitor/NSAID use before the event/index date and the outcome event, current use was not associated with a decrease in schizophrenia case events (adjusted OR 1.16; 95%CI 0.83-1.62).

TABLE 1 – Characteristics of cases and controls

	CASES n=1443 (100%)	CONTROLS n=1443 (100%)
Mean age at event/index date [SD]	55.3 [14.1]	57.1 [13.3]
Male sex	623 (47.9%)	678 (47.2%)
Co-morbidities, ≥ 1 diagnosis after 1 January 1992		
Dementias – ICD 290	128 (8.9%)	83 (5.8%)
Alcohol-induced mental disorders – ICD 291	43 (3.0%)	27 (1.9%)
Drug-induced mental disorders – ICD 292	47 (3.3%)	24 (1.7%)
Transient mental disorders due to other conditions – ICD 293	164 (11.4%)	132 (9.1%)
Persistent mental disorders due to other conditions – ICD 294	133 (9.2%)	99 (6.9%)
Episodic mood disorders – ICD 296	1101 (76.3%)	958 (66.4%)
Delusional disorders – ICD 297	180 (12.4%)	126 (8.7%)
Other nonorganic psychoses – ICD 298	556 (38.5%)	433 (30.0%)
Pervasive developmental disorders – ICD 299	8 (0.6%)	5 (0.3%)
Drug use (in 365 days before event/index date)		
Oncolytics	22 (1.5%)	26 (1.8%)
Corticosteroids	153 (10.6%)	129 (8.9%)
Lipid lowering drugs	289 (20.0%)	323 (22.4%)
Cardiac drugs (e.g. digoxin)	173 (12.0%)	153 (10.6%)
RAAS inhibitors	315 (21.8%)	304 (21.1%)
Acid lowering drugs	427 (29.6%)	348 (24.1%)
Antiepileptics	578 (40.1%)	413 (28.6%)
Antidiabetic drugs	265 (18.4%)	232 (16.1%)
Drugs used for the treatment of Parkinson's disease	385 (26.7%)	328 (22.7%)
Drugs used for the treatment of mania	170 (11.8%)	161 (11.1%)
Antidepressants	881 (61.1%)	700 (48.5%)

SD = standard deviation; ICD = International Classification of Diseases; RAAS = renin-angiotensin-aldosterone system

TABLE 2 – Number of patients with the various types of medication (case) events in the cohort (n=1443)

	Patients with the event (%)
Use of a parenteral antipsychotic	33 (2.3%)
Switch to a different antipsychotic	372 (25.8%)
Start combination therapy	325 (22.5%)
Dose increase >30%	713 (49.4%)

TABLE 3 – The association between the risk for deterioration of schizophrenia and type or cumulative level of COX-2 inhibitor/NSAID exposure: nested case-control analysis

	CASES n=1443	CONTROLS n=1443	Crude OR (95%CI)	Adj OR[a] (95%CI)
CURRENT/RECENT EXPOSURE:				
None	1147	1203	Reference	Reference
COX-2 inhibitor recent				
0–93 days total	39	13	3.15 (1.67–5.93)	2.56 (1.35–4.87)
94–324 days total	17	22	0.81 (0.43–1.54)	0.74 (0.39–1.42)
>324 days total	20	9	2.33 (1.06–5.14)	2.22 (0.99–4.98)
COX-2 inhibitor current				
0–93 days total	26	13	2.10 (1.07–4.10)	1.83 (0.92–3.64)
94–324 days total	26	28	0.97 (0.57–1.67)	0.98 (0.57–1.70)
>324 days total	34	33	1.08 (0.67–1.76)	1.03 (0.63–1.70)
NSAID recent				
0–93 days total	43	38	1.19 (0.76–1.85)	1.00 (0.64–1.57)
94–324 days total	9	16	1.57 (0.56–4.43)	1.38 (0.48–3.93)
>324 days total	15	10	1.57 (0.70–3.52)	1.51 (0.67–3.43)
NSAID current				
0–93 days total	15	15	1.05 (0.51–2.16)	0.91 (0.44–1.90)
94–324 days total	5	10	0.52 (0.18–1.54)	0.47 (0.16–1.41)
>324 days total	24	30	0.84 (0.49–1.44)	0.84 (0.48–1.46)
CUMULATIVE EXPOSURE IN DDDs, 90 DAYS BEFORE INDEX DATE:				
None	1149	1203	Reference	Reference
COX-2 inhibitor only				
1–45 DDDs	44	30	1.97 (1.29–3.09)	1.78 (1.15–2.80)
46–90 DDDs	31	42	1.28 (0.86–1.91)	1.24 (0.82–1.87)
>90 DDDs	35	37	1.15 (0.75–1.77)	1.02 (0.65–1.58)
NSAID only				
1–30 DDDs	61	32	1.54 (0.96–2.46)	1.40 (0.87–2.26)
31–75 DDDs	55	45	0.77 (0.48–1.24)	0.68 (0.42–1.10)
>75 DDDs	45	41	0.99 (0.62–1.58)	0.91 (0.56–1.47)
Combined NSAID and COX-2 inhibitor	23	13	1.85 (0.93–3.67)	1.68 (0.84–3.38)

COX-2 = cyclooxygenase-2; NSAID = non-steroidal anti-inflammatory drug; DDDs = defined daily doses

a) Adjusted odds ratios (Adj ORs) are based on multivariate logistic regression models including age, sex and use of antiepileptics, antidepressants, drugs used for the treatment of Parkinson's disease or corticosteroids in the year before the index date.

Table 3 shows the results of the analysis in more detail for the different exposure durations and levels. Recent COX-2 inhibitor users with a duration of use of 0 to 93 days, had an increased risk for the deterioration of their disease (adjusted OR 2.56; 95%CI 1.35-4.87). No relation was found for NSAIDs.
When the data were analysed for the different levels of recent exposure in Defined Daily Doses (DDDs), we found an association between the use of COX-2 inhibitors and an increased risk for unfavourable medication events for the 0-45 DDD group (adjusted OR 1.78; 95%CI 1.15-2.80). Other NSAIDs did not show a significant association in the crude or adjusted analysis at any exposure level.
When stratifying the results for recent use according to the type of COX-2 inhibitor, we found that rofecoxib, the most selective COX-2 inhibitor of the compounds in this study, showed a stronger association between recent use and deterioration of schizophrenia (adjusted OR 2.88; 95%CI 1.29-6.43) than celecoxib (adjusted OR 1.29; 95%CI 0.82-2.03).

DISCUSSION

Our results do not provide evidence for the hypothesis that the use of COX-2 inhibitors is associated with a favourable effect on schizophrenia. Instead, we found a significant association between the discontinuation of COX-2 inhibitors in the 90 days before the event date and deterioration of the disease state.
The mechanism behind the supposed beneficial effect of COX-2 inhibitors in schizophrenia is still unresolved. In general, two theories can be identified.[8] The first theory focuses on the role of cyclooxygenase-2 in immunological processes: COX-2 inhibitors may reduce the levels of cyclooxygenase-2 up-regulated cytokines in the brain, such as IL-2, IL-6, IL-10 and TNF-alpha, and thereby reduce inflammatory processes that have been associated with schizophrenia. However, clinical studies have not been able to substantiate this mechanism.[9,10] A second theory states that COX-2 inhibitors modify the glutamergic signalling pathway, reducing the over-activation of NMDA receptors, which have been implicated in the pathogenesis of schizophrenia.
These two theories cannot explain our finding that recent use of COX-2 inhibitors was associated with a deterioration of schizophrenia. A hypothesis from

the cardiovascular field may account for the findings in this study. It has been hypothesised that the adverse effects seen in the COX-2 inhibitor class, and which precipitated the market withdrawal of rofecoxib, may be caused by a 'compensatory host response'.[11] Under this hypothesis, the withdrawal of cyclooxygenase-2 inhibition after discontinuation of a COX-2 inhibitor leads to a sudden increase in the activity of cyclooxygenase-2 mediated processes. When applied to schizophrenia, the withdrawal of a COX-2 inhibitor would thus increase cyclooxygenase-2 activity, influencing the inflammatory and neurotransmission pathways related to schizophrenia. To further investigate this, we also studied the association between the duration of prior COX-2 inhibitor use and the deterioration of schizophrenia disease status. However, since we found no statistically significant relation in this analysis, we cannot substantiate the 'compensatory host response' theory. Thus, the most likely explanation is a false positive finding related to multiple hypothesis testing.

A fourth hypothesis could be that COX-2 inhibitors do have a protective effect and that withdrawal of this 'protection' leads to a sudden deterioration in health status. However, our data do not allow us to explore this hypothesis in detail.

Within the class of COX-2 inhibitors, there is strong variation in the COX-1/COX-2 ratio for cyclooxygenase-isoform activity, with rofecoxib being a more selective inhibitor of cyclooxygenase-2 than celecoxib. Furthermore, rofecoxib also has a higher brain penetrance. However, the analysis for rofecoxib and celecoxib showed a similar pattern to the overall results.

When interpreting the results of this study, there are some limitations that have to be taken into account. Firstly, we used changes in antipsychotic medication as the outcome measure. In clinical trials, the beneficial effects of celecoxib were seen when the PANSS-scale was used as the main outcome measure. A non-scale outcome, such as the medication events evaluated here, may be unsuitable for detecting clinically small effects. However, we believe that the selected outcome events constitute a meaningful measure of schizophrenia deterioration in an observational setting and can provide information about the effects of drug use or other interventions. For individual outcomes, we find support for our assumption in earlier studies. For example, our hypothesis that switching is an indicator for disease deterioration can be substantiated by an earlier study that showed that switching is often caused by a lack of therapeutic effect or adverse effects.[12] In our study, case events were preceded by a continuous follow-up period of at least 90

days, making switching because of adverse events which occur soon after the start of therapy less likely. Therefore, lack of effect seems to be the most plausible reason for a medication switch. We have assumed that lack of therapeutic effect is also the most important reason for the other medication events.

In future observational studies it may be worthwhile to look at other outcome measures besides medication use such as hospitalisations, which were not included in this study because of unreliable coding in the database.

Furthermore, the information available about patient characteristics was limited. Validation of diagnoses is a challenging aspect of observational database studies. We tried to minimise misclassification by requiring patients to have at least three prescriptions for an antipsychotic in addition to having a diagnosis of schizophrenia based on first three digits of the ICD-9 code. Also, it was not possible to reliably determine the time since the first schizophrenia diagnosis or disease severity, which may be a relevant factor for the effects of COX-2 inhibitors in this disease. In one of the clinical trials, recently diagnosed patients showed more improvement when celecoxib was added to an antipsychotic treatment than patients for whom the diagnosis was made a longer time ago.[13] The peak incidence of schizophrenia is between 20-30 years of age; the median age of our population was 55.3 years for the cases and 57.1 years for the controls. Similarly, the patients studied in a claims database may be in the later stages of their disease, have late-onset schizophrenia, or have a relatively stable disease. The median follow-up to first medication event of 302 days may indicate stable disease. This may not be the population in which COX-2 inhibitors have a beneficial effect on schizophrenia disease status. Further observational research might be done on datasets that allow more detailed categorisation of schizophrenia.

A third limitation is the nature of the data source used. Since IMS-Lifelink is a claims database, we may not have captured all drug use by patients. This may especially be the case for over the counter non-selective NSAIDs. However, if this exposure misclassification has occurred, we believe that it is nondifferential with regards to the cases and controls and therefore will not have influence the outcome of this study in a major way. The non-selective NSAIDs are known to vary in their COX-2 inhibitor selectivity; future studies could also further categorise non-selective NSAIDs.

Furthermore, Lifelink is an employee claims database containing information about employees and their dependants. This makes it likely that patients in this database have a higher socioeconomic status than the average patient with schizophrenia. However, we have no evidence to suggest that socioeconomic status is associated with the effectiveness of COX-2 inhibitors and NSAIDs in preventing the deterioration of schizophrenia.

In conclusion, the use of COX-2 inhibitors was not associated with a decreased risk for the deterioration of schizophrenia in this observational study. However, the observational design may limit the generalisation of this finding. Future studies could look into this effect in more detail, as well as the effects of COX-2 inhibitors in certain patient subgroups, such as those who were recently diagnosed.

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chapter 4.2

Taking low dose aspirin is associated with more stable drug treatment for lithium users

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ABSTRACT

Introduction

Mood stabiliser administration to rats downregulates markers of brain arachidonic acid (AA) metabolism, including phospholipase A2 (PLA2) and cyclooxygenase (COX). Some evidence indicates that the AA cascade is upregulated in bipolar disorder (BD). We hypothesise that agents targeting the AA cascade will ameliorate BD symptoms.

Methods

We collected medication histories of patients who had been prescribed lithium from the PHARMO database. Data were stratified according to drug classes that inhibit PLA2 and/or COX enzymes and duration of use. Incidence density (ID) of BD medication events (dose increases/substance changes) was used as a proxy for BD deterioration. ID ratios in patients with COX and/or PLA2 inhibitors next to lithium were compared to ID ratios in patients using lithium alone.

Results

Low-dose aspirin significantly reduced the ID ratio of medication events, independent of duration of use. The ID ratio of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids was not different from 1.0 if prescribed for ≥180 or ≥90 days, but significantly exceeded 1.0 when shorter durations of use were included. Selective COX-2 inhibitors had no significant effect and multiagent administration increased the ID ratio above 1.0.

Conclusion

Clinical diagnosis and disease deterioration was based on prescription records. Some over-the-counter drug use may not have been captured. Patients using low-dose aspirin may have represented a uniquely compliant subgroup. The increased ID ratios for NSAIDs, glucocorticoids and combined inhibitors, may reflect confounding by indication.These preliminary neuroepidemiological results indicate that low-dose aspirin may ameliorate symptoms of BD patients taking lithium, warranting further studies.

INTRODUCTION

Bipolar disorder is characterised by episodes of mania alternated with episodes of depression and periods of euthymia. Its 12-month prevalence is about 1%, and its cumulative lifetime prevalence has been estimated to lie between 1.5% and 2.0%.[1] The lifetime suicide rate in the disease is 10-20%.[2] Bipolar disorder has multiple risk alleles consistent with a polygenic inheritance,[3] but its pathological mechanisms are poorly understood.

Lithium has been one of the first-line treatments of bipolar disorder for over 50 years; the anticonvulsants carbamazepine, valproic acid, lamotrigine and several antipsychotics (most importantly, olanzapine and quetiapine) are more recent therapeutic options.[4,5] Multiple mechanisms for the action of these agents have been suggested, including the inositol depletion hypothesis and inhibition of glycogen synthase kinase-3 for lithium; inhibition of histone deacetylation for valproic acid; and modulation of sodium channels, adenosine receptors and adenylate cyclase for carbamazepine.[6] However, none of these mechanisms is agreed upon.

A mechanism recently suggested by Rapoport and colleagues,[7-9] based on studies in rats, is that chronic lithium, valproic acid and carbamazepine commonly downregulate the brain arachidonic acid (AA, 20:4n-6) cascade, including phospholipase A2 (PLA2) and cyclooxygenase (COX) enzymes.[9,10] These enzymes, respectively, induce the release of AA from membrane phospholipid and convert it to bioactive molecules such as prostaglandin E2 and thromboxane B2. The AA cascade is involved in neuroreceptor-initiated signalling in the normal brain and can be pathologically upregulated by neuroinflammation and excitotoxicity.[11,12] Some evidence indicates that the AA cascade is upregulated in the brain of patients with bipolar disorder.[13]

In this study, we tested the hypothesis that drugs that can interfere with the brain AA cascade are beneficial in bipolar disorder. We assessed the association between exposure to inhibitors of PLA2 and/or COX enzymes and symptom worsening in patients treated with lithium, when taking lithium treatment as a surrogate marker of bipolar disorder. We estimated symptom worsening in a pharmacoepidemiological research database, based on changes in the dispensing of concomitant medication used in the treatment of bipolar disorder next to lithium.

METHODS

Study setting

The setting was the PHARMO Record Linkage System (RLS) in the Netherlands. This system contains pharmacy dispensing records from community pharmacies linked to hospital discharge records of more than two million community-dwelling residents in more than 25 population-defined areas in the Netherlands from 1985 onwards.[14] Since nearly all people in the Netherlands are registered with a single community pharmacy, independent of prescriber, their pharmacy records are virtually complete with regard to prescription drugs.

The computerised drug dispensing histories in the PHARMO RLS contain information on the dispensed drug, dispensing date, prescriber, amount dispensed and the prescribed dosage regimen. Each patient is registered with an anonymous unique patient identification code that allows for the observation of patient medication over time. All medicines are coded according to the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification system.[14,15] The database, however, does not provide information concerning the indications (e.g. disease or diagnosis) for the use of medicines. Our study covered the 10-year period from 1 January 1996 to 31 December 2005.

Cohort selection

We selected all patients of at least 18 years of age who had been dispensed at least five prescriptions for lithium and who had at least one year of drug dispensing history prior to inclusion. Follow-up started on the day of the first dispensing of a lithium prescription and ended on the theoretical end date of the last prescription. A maximum gap between the theoretical end date of a prescription and the dispensing date of the next prescription of 90 days was accepted. More than one period of follow-up per patient was possible.

Exposure

To determine whether subjects were exposed to inhibitors of the brain's AA cascade during follow-up, exposure episodes were constructed for each individual subject based on the theoretical end date of a prescription (based on the prescribed dose and the amount dispensed).

The following six classes of inhibitors of brain COX and/or PLA2 were evaluated:

1. Acetylsalicylic acid (aspirin) at a low dose of 30 mg or 80 mg (a preferred inhibitor of COX-1, an acetylator of COX-2);[16]
2. Acetylsalicylic acid at high dose (>80 mg);
3. Non-selective non-steroidal anti-inflammatory drug (NSAIDs, inhibitors of both COX-1 and COX-2), excluding acetylsalicylic acid and selective inhibitors of COX-2;
4. COX-2 selective inhibitors;
5. Glucocorticoids for systemic use (inhibitors of PLA2 and COX enzymes);
6. More than one inhibitor type (among 1-5).

We evaluated the data using different minimum durations for an episode: ≥1 day, ≥45 days, ≥90 days, and ≥180 days.

Outcomes of interest

For each subject having been dispensed lithium, we examined medication 'events' in the dispensing history that we considered to be a proxy for deterioration of bipolar disorder. Medication events were evaluated with regard to prescribing the following five classes of drugs, based on ATC codes:[15]

1. Anxiolytics (N05B);
2. Hypnotics and sedatives (N05C);
3. Antipsychotics (N05A), except lithium (N05AN);
4. Antidepressants (N06A);
5. Other drugs (mood stabiliser anticonvulsants)[17] used in treating bipolar disorder (valproic acid [N03AG01], carbamazepine [N03AF01], and lamotrigine [N03AX09]).

Within these five drug classes, the following medication events were evaluated as an indication for the deterioration of the underlying psychiatric disease:

- *Substance change*: Introduction of a new active substance used by the patient. 'New' is defined as a substance that was not dispensed in the prior 180 days. In practice, this indicates medication switching, or the start of combination therapy.
- *Dose change*: An increase in the calculated daily dose of a substance of >30%, compared to the prior prescription. This increased dose, or a higher dose, must not have been used in the previous 180 days.

To determine whether the number of medication events taken as a proxy for disease deterioration varied between the different exposure groups, we calculated

the incidence density (ID) of medication events for each exposure episode. The ID was defined as the number of medication events divided by the total duration of the follow-up episode expressed in person years.

Potential risk factors

Several cofactors were assessed that may have influenced the outcome of interest. Age at the start of the episode and sex were included as baseline patient characteristics. As a measure of total health care utilisation, we calculated the total number of prescriptions for all drugs dispensed to a patient during an episode. Patients were assigned to one of three categories of health care utilisation (low, medium, or high), based on tertiles. As a measure of chronic disease burden we determined the Chronic Disease Score, which is a measure of chronic disease status based on dispensing records.[18-20] We calculated this score based on the drugs dispensed during the year prior to an exposure episode. Patients were classified according to their Chronic Disease Score in three categories (0 points, 1-3 points, >3 points).

To determine the possible influence of COX selectivity, we also compared crude ID ratios of NSAIDs at the substance level. We divided the NSAIDs into groups, based on their COX selectivity according to a comparative analysis by Warner et al.[21] A sub-analysis was also performed for the COX-2 inhibitor group, focussing on whether the ability to penetrate the blood-brain barrier was of influence. Rofecoxib and valdecoxib are reported to achieve a therapeutic plasma concentration in the central nervous system, leading to COX-2 inhibition, whereas the concentration reached by celecoxib is too low for therapeutic effects.[22]

Data analysis

IDs for the different exposure groups were compared by calculating ID ratios, with patients using lithium alone as the reference group, with 95% confidence intervals. Poisson logistic regression was used to adjust for the influence of covariates.

RESULTS

As illustrated in Table 1, a total of 5145 subjects (38.5% male and 61.5% female) who were prescribed a lithium-containing drug fulfilled our initial criteria for

inclusion in the study. Their average age of entry into the database was 48.6 ± 15.1 (SD) years, and their average length of an episode of lithium use was 847.1 days. Within the 10 year period of observation, follow up started in 30.0% of the patients when <40 years of age, 22.7% when >60 years, the remainder was between 41 and 60 years.

TABLE 1 – Baseline characteristics of lithium users and number of medication events during lithium use, categorized according to drug classes

BASELINE CHARACTERISTICS	N=5145 (100%)
Sex:	
▪ male	1983 (38.5%)
▪ female	3162 (61.5 %)
Average age in years [SD] (on first lithium Rx during follow-up)	48.6 [15.1]
Age at start of first episode in years:	
▪ <40	1546 (30.0%)
▪ 41–60	2430 (47.3%)
▪ >60	1169 (22.7%)
Average duration of exposure episode	847.05 days
MEDICATION EVENTS	**SUBSTANCE CHANGE / DOSE CHANGE**
All groups	6904 / 9530
1. anxiolytics	1469 / 2339
2. hypnotics and sedatives	1630 / 1236
3. antipsychotics	1782 / 2467
4. antidepressants	1885 / 2746
5. other drugs used in the treatment of bipolar disorder	138 / 742

SD = standard deviation

Table 2 summarises the number of medication 'events' suggestive of disease worsening, person years, ID and crude and adjusted ID ratios (with 95% confidence intervals) for lithium and each of the six exposure classes under investigation. The adjusted ratios are corrected for age category, sex, Chronic Disease Score and health care utilisation by including them as categorical variables in the Poisson regression model. The data are stratified according to minimum duration of exposure to AA cascade inhibitors. Statistically significant ID ratios at $p<0.05$ are indicated in bold. ID ratios were significantly less than 1.0

TABLE 2 – Medication events, person years, incidence density, and incidence density relative to lithium at different minimum exposure durations to inhibitors of phospholipase A2 and/or cyclooxygenase enzymes

EXPOSURE HISTORY	EVENTS	PERSON YEARS	ID	ID RATIO TO LITHIUM ONLY (95%CI)[a] Crude	Adjusted[b]
NO EXPOSURE:					
Lithium only	15 365	19 241	0.799	Reference	Reference
≥ 45 days	15 271	19 220	0.795	Reference	Reference
≥ 90 days	15 096	19 156	0.788	Reference	Reference
≥180 days	14 330	18 780	0.763	Reference	Reference
EXPOSURE TO:					
Low dose ASA (30 or 80 mg/day)	360	543.96	0.662	**0.83 (0.75 – 0.92)**	**0.86 (0.77 – 0.96)**
≥ 45 days	355	541.13	0.656	**0.83 (0.74 – 0.92)**	**0.86 (0.77 – 0.95)**
≥ 90 days	344	537.61	0.640	**0.81 (0.73 – 0.90)**	**0.84 (0.75 – 0.93)**
≥180 days	329	525.39	0.626	**0.82 (0.74 – 0.92)**	**0.84 (0.75 – 0.94)**
High dose ASA (>80 mg/day)	33	32.32	1.021	1.28 (0.91 – 1.80)	1.33 (0.94 – 1.87)
≥ 45 days	24	23.64	1.015	1.28 (0.86 – 1.91)	1.24 (0.83 – 1.85)
≥ 90 days	23	20.54	1.120	1.42 (0.94 – 2.14)	1.33 (0.88 – 2.00)
≥180 days	13	15.01	0.866	1.14 (0.66 – 1.96)	1.03 (0.60 – 1.77)
Non-selective NSAIDs	525	471.70	1.113	**1.39 (1.28 – 1.52)**	**1.52 (1.39 – 1.66)**
≥ 45 days	415	402.28	1.032	**1.30 (1.18 – 1.43)**	**1.37 (1.24 – 1.51)**
≥ 90 days	338	361.91	0.934	**1.19 (1.06 – 1.32)**	**1.21 (1.09 – 1.35)**
≥180 days	255	305.39	0.835	1.09 (0.97 – 1.24)	1.09 (0.97 – 1.24)
COX-2 selective inhibitors	19	19.61	0.967	1.21 (0.77 – 1.90)	1.40 (0.89 – 2.20)
≥ 45 days	14	15.35	0.912	1.15 (0.68 – 1.94)	1.29 (0.76 – 2.18)
≥ 90 days	14	13.20	1.061	1.35 (0.80 – 2.27)	1.43 (0.85 – 2.41)
≥180 days	10	9.98	1.002	1.31 (0.71 – 2.44)	1.44 (0.77 – 2.68)
Glucocorticoids	83	64.80	1.281	**1.60 (1.29 – 1.99)**	**1.62 (1.30 – 2.01)**
≥ 45 days	69	58.52	1.179	**1.48 (1.17 – 1.88)**	**1.48 (1.17 – 1.87)**
≥ 90 days	52	52.08	0.998	1.27 (0.96 – 1.66)	1.23 (0.94 – 1.62)
≥180 days	39	43.75	0.891	1.17 (0.85 – 1.60)	1.12 (0.82 – 1.54)
More than one inhibitor type	45	31.12	1.446	**1.81 (1.35 – 2.43)**	**1.90 (1.42 – 2.55)**
≥ 45 days	42	26.92	1.560	**1.96 (1.45 – 2.66)**	**2.01 (1.48 – 2.73)**
≥ 90 days	33	23.05	1.432	**1.82 (1.29 – 2.56)**	**1.79 (1.27 – 2.53)**
≥180 days	29	17.39	1.668	**2.19 (1.52 – 3.15)**	**2.08 (1.44 – 3.00)**

ID = incidence density, defined as number of events/person year; ASA = acetylsalicylic acid; NSAIDs = non-steroidal anti-inflammatory drugs; COX-2 = cyclooxygenase-2

a) Statistically significant ID ratios at $p<0.05$ are indicated in bold.

b) Adjusted for age category, sex, Chronic Disease Score and health care utilisation.

for low dose acetylsalicylic acid prescribed for an unspecified time or for ≥1, ≥45, ≥90 or ≥180 days. ID ratios were significantly greater than 1.0 for NSAIDs excluding COX-2 inhibitors prescribed for ≥1, ≥45 or ≥90 days, but not for ≥180 days. They were significantly greater than 1.0 for glucocorticoids prescribed for ≥1 or ≥45 days, but did not differ from 1.0 when glucocorticoids were dispensed for ≥90 or ≥180 days. The ID ratios were significantly greater than 1.0 for administration of more than one AA cascade inhibitor at all treatment times, but did not differ from 1.0 for acetylsalicylic acid (excluding low dose acetylsalicylic acid) or for COX-2 inhibitors prescribed for ≥1, ≥45, ≥90 or ≥180 days.

We also determined crude ID ratios of NSAIDs, divided according to COX selectivity based on a comparative analysis by Warner et al.[21] (data not shown). We found no statistically significant effect of COX selectivity on the ID ratio, when the drugs were prescribed for an unspecified time.

Additionally, we looked at differences between COX-2 inhibitors based on their reported ability to penetrate the blood-brain barrier.[22] In a sub-analysis at the substance level for the COX-2 inhibitors, the unadjusted relative risk was 2.69 (CI 95%: 0.87-8.36) for rofecoxib and 1.24 (CI 95%: 0.75-2.06) for celecoxib, not taking into account duration of use. There were too few prescriptions for valdecoxib in the dataset to calculate a relative risk.

DISCUSSION

This pharmacoepidemiological study on patients treated with lithium does not establish an association between the use of the whole class of drugs that inhibits PLA2 and/or COX enzymes and amelioration of bipolar disorder symptoms. However, the adjusted ID ratio was significantly less than 1.0 for subjects who had been dispensed low-dose aspirin in addition to lithium. In contrast, use of NSAIDs (excluding COX-2 inhibitors), as well as of glucocorticoids, resulted in ID ratios significantly above 1.0 when prescribed for ≥180 days and ≥90 days, but ID ratios did not differ from 1.0 when episodes of a shorter duration were included in the analysis. There was no significant effect of COX selectivity on the ID ratio.

That low-dose aspirin decreased the number of medication events, i.e., reduced the ID ratio when compared to the ratio of lithium treatment alone, irrespective of prescription duration, is consistent with the hypothesis that inhibitors of brain PLA2 and/or COX enzymes would be beneficial in bipolar disorder.[8,9] Furthermore, this finding is in line with the results of a study indicating that acetylsalicylic acid produced positive mood-modulating effects in men undergoing coronary angiography.[23] Thus, the decreased ID ratio associated with use of low-dose aspirin may have reflected a direct effect on the disease state in bipolar disorder. However, taking low-dose acetylsalicylic acid may characterise conscientious, organised individuals concerned about the prophylaxis of coronary disease, the major reason for prescribing low-dose aspirin. Such personality characteristics are unlikely in patients with more severe bipolar disorder, who are poorly compliant. This so called 'healthy user' bias may have influenced our results.[24] Our data are insufficient to resolve this issue.

In contrast, our finding that short-term NSAIDs and glucocorticoids increased the ID ratio appears inconsistent with the AA cascade hypothesis. One explanation for the discrepancy, illustrated by the duration of use analysis, is that an AA cascade inhibitor must be given for a longer period of time to produce a positive effect in bipolar disorder. Another explanation is that aspirin, NSAIDs and glucocorticoids have different mechanisms of action and ancillary effects. For example, aspirin is considered to inhibit COX-1 activity much more than COX-2 activity,[25,26] to downregulate transcription of the COX-2 gene [27] and to acetylate COX-2 protein to a modified enzyme that can convert unesterified AA to anti-inflammatory mediators such as 15-epi-lipoxin A4.[28] Glucocorticoids may inhibit PLA2 and prostaglandin formation by inducing the formation of lipocortin-1, but glucocorticoids have a number of effects that may aggravate bipolar disorder.[29-31]

A third explanation would be that the increased ID ratios for NSAIDs and glucocorticoids at the shorter prescription times represented 'confounding by indication'.[32,33] The clinical indication for prescribing the drugs may also be associated with a more severe disease state for bipolar disorder, as well as alternative comorbidities. For example, NSAIDs are prescribed for rheumatoid arthritis, and both the disease and the drugs themselves are known to potentially increase psychiatric symptoms.[34,35] We could not fully correct for this by including the Chronic Disease Score in our model.

Although NSAIDs can increase lithium serum levels into the toxic range, this was not likely to be the cause of the increased relative risk that was found in this study. The toxic effects of lithium (e.g. tremor, diarrhoea nausea, vomiting and renal effects) are not easily confused with acute episodes in bipolar disorder, and are therefore not likely to result in changes in the prescribing of the drug classes that were used as a proxy for deterioration of bipolar disorder in this study.

When interpreting our results, several limitations of this study should be taken into account. Firstly, we were unable to validate the diagnosis of bipolar disorder, and lithium may alternatively have been prescribed for other indications, mainly unipolar depression.[36-38] However, when we performed an analysis excluding individuals who had been prescribed an antidepressant in the year before their first lithium prescription in the database, we did not find changes in the direction of effect for the calculated relative risks. Furthermore, no beneficial psychiatric effect for the drug classes of interest in this study regarding unipolar depression has been established, and thus this misclassification would rather lead to a bias towards the null hypothesis.

Secondly, the outcome that was taken as a proxy for disease deterioration was a change in medications used in the treatment of bipolar disorder. We have used this measure elsewhere to quantify disease deterioration,[39] but it is limited since no data on actual clinical symptoms were available. Future studies should include clinical outcomes, such as suicides, bipolar rating scales (Young Mania Rating Scale [YMRS]), psychiatric hospitalisations and total health care utilisation (including number of doctor visits and the type of medical interventions).

Also, in the Netherlands some NSAIDs (e.g. ibuprofen and diclofenac) are available as non-prescription 'over-the-counter' medicines. This use was not captured in our database, since it only contains information for prescription drugs. However, it is likely that any misclassification resulting from this is random with regard to the outcome and would therefore lead to a bias towards the null.

In conclusion, our results tentatively support the hypothesis [7-9] that drugs that inhibit PLA2 and/or COX enzymes of the AA cascade could ameliorate the symptoms of bipolar disorder. This evidence was the duration-independent significant reduction in the relative risk of disease deterioration (ID ratio to lithium alone) in subjects prescribed low-dose acetylsalicylic acid. Future studies should be based on larger cohorts with a longer duration of use of enzyme

inhibitors and more detailed information about the diagnosis and clinical course of disease, and should include controlled clinical trials.

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General discussion

chapter 5

THE *P*OST-*I*NNOVATION *L*EARNING CYCLE FOR PHARMACEUTICA*LS* (*PILLS*)

The first chapter of this thesis started with the notion that in the pharmaceutical arena three goals have to be balanced constantly by regulators and policy makers: ensuring patient access to safe and effective medicines, allocating scarce resources in an optimal way, and rewarding innovation.

How to achieve these goals is an integral part of the discussion about the major challenges that we are currently facing in the field of pharmaceuticals. These challenges include: rising drug expenditures, a lack of trust in the safety monitoring system, and increasing development costs with a decreasing number of new drugs coming to the market.[1-3] In this debate, a wide variety of actors meet: a supply side represented by multinational corporations and a demand side consisting of local health care providers and patients, health insurers, and policy makers with diverging views on what constitutes a fair and just pharmaceutical marketplace. The interactions between these key actors vary across regions and countries, thus leading to many different proposed solutions and a plethora of access and reimbursement systems, drug usage patterns and incentive measures for drug innovation. This variability constitutes a rich opportunity for learning and identifying avenues for improvement.

In the present thesis our aim was to contribute to the development of a set of analytical tools to study the usage environment as a so-called post-innovation learning cycle for pharmaceuticals. In this chapter we will place our findings in a broader perspective. Furthermore, we will give recommendations on how pharmaceutical policies can be evaluated and improved.

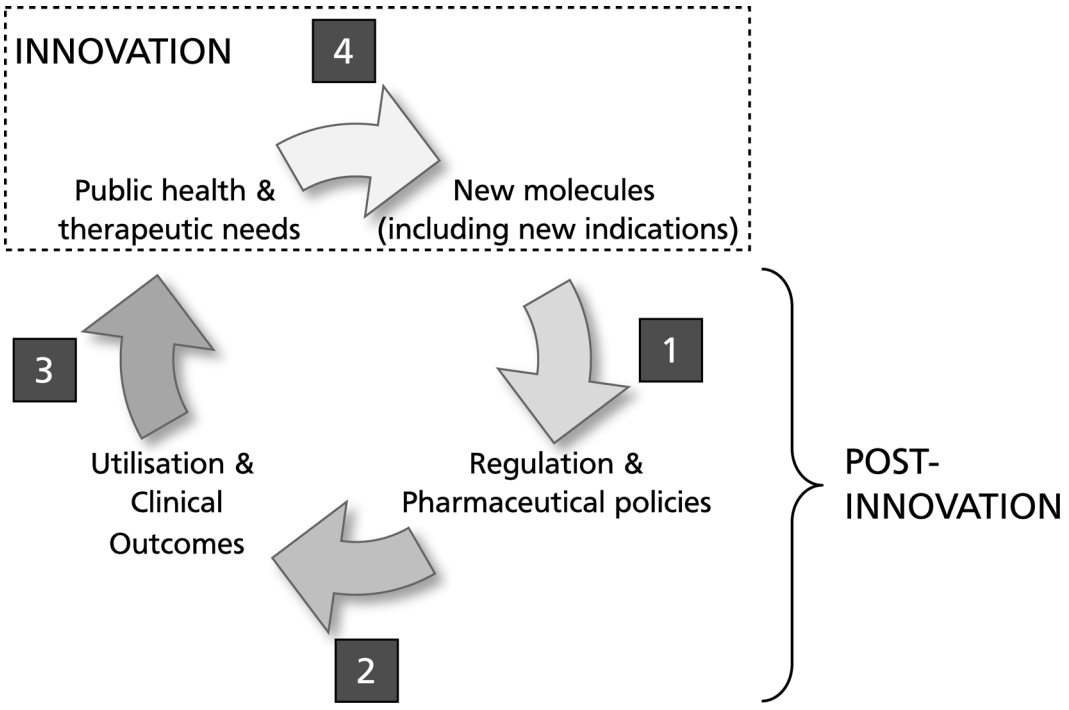
LESSONS FROM STUDIES ON THE POST-INNOVATION LEARNING CYCLE

The framework that was presented in Chapter 1 is shown again in Figure 1. Here we focus on the post-innovation section of this learning cycle.

The first section in the post-innovation cycle relates to the embedding of a new drug or a new application for an existing drug in the regulatory and health system (*Section 1*). For example, payers have to determine whether or not a drug will be reimbursed, and professional organisations have to make up their mind

about the role of a new medicinal product in clinical practice.[4,5] In the next section of the cycle, the medicinal product is taken up and used in clinical practice (*Section 2*). Usage is heavily influenced by policy interventions and a changing landscape of incentives. Based on the outcomes of treatment, the therapeutic needs of the population may change (*Section 3*). Furthermore, using drugs in clinical practice may provide leads for new applications, providing incentives for pharmaceutical research and development.[6] It should be emphasized that this post-innovation learning cycle is not meant to be an exhaustive or limitative description. Rather, it is a conceptual framework to illustrate how different aspects of the usage environment are interconnected and how different tools can be used to study these links. In the next three paragraphs we will discuss our findings in this study in relation to the different sections in the learning cycle.

FIGURE 1 - A proposed learning cycle for pharmaceuticals



Embedding new drugs in the health system (*Section 1*)

One of the great challenges of modern health systems is how to embed new technologies, such as pharmaceuticals, in the system in an efficient, fair and sustained fashion. For example, in most health systems an assessment procedure is required before a medicinal product can be reimbursed by insurers (e.g. by determining whether or not a drug is included on a 'positive list').[5,7] During this assessment, regulators and policy makers are confronted with a wide variety of drug classes, sometimes with new working mechanisms or molecular properties and intended for a variety of diseases. Notwithstanding this variability, each drug has to be assessed according to, and included in, an existing framework of rules and regulations. In this section, we discuss two problems that may arise: the impact of the design and properties of the pre-marketing phase on post-marketing regulation, and how to embed drugs that are expensive and/or targeted to specific populations, such as orphan drugs.

At the moment of initial assessment, almost all information that is available about the drug is based on pre-clinical and pre-marketing investigations. From several studies it is known that the populations and dosages in clinical trials may be very different from actual clinical practice.[8-13] Therefore, it is relevant to know which drugs are most susceptible to undergo the changes in their application from the pre- to the post-marketing phase. In this thesis we discuss one of the examples mentioned above in some more detail: are there certain molecular properties of a drug that are associated with post-marketing dose changes?

Post-marketing changes in recommended dosages appear to be a common occurrence affecting about one in five new medicinal products.[14,15] In Chapter 2.1 we show that being a substrate for CYP2D6/CYP3A metabolism makes drugs more likely to undergo a post-marketing change in the Defined Daily Dose, a dosage measure set by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology.[16] In many drug price setting systems, the daily dose of a drug is used as a basis for making price comparisons between drugs, meaning that these dosage changes can also have implications for regulation.[17] Thus, molecular properties of a drug can be linked to drug characteristics that may influence pricing and reimbursement policies.

Of course, the metabolism pathway is but one of the many properties of a drug in development that can influence regulatory environment. Also, certain drug classes may be more susceptible to dosage changes than others.[18] Moreover,

future developments in the fields such as genetics may radically alter patient stratification and treatment allocation in clinical trials, and thus the evidence that is available at market entry.[19] Regulators should take these developments into consideration and closely monitor early post-marketing developments in drug use for their possible implications for drug regulation. Pharmacoepidemiological information about which patients use the newly introduced drug can play a pivotal role in learning about the life events of a new medical product.

Another important challenge is how to handle the embedding of drugs that are expensive and/or targeted at specific populations. Due to developments such as the 'stratification' of the patient population, this topic is likely to feature prominently on future policy agendas.[20] One well-known drug class in this respect are drugs intended for the treatment of rare diseases, so-called orphan drugs. Although the definition of what constitutes a rare disease differs somewhat between the European Union (EU) and the United States of America (USA), in general rare diseases are those with a prevalence <7.5 : 10 000 persons. Orphan drugs are a relatively recent phenomenon, only reaching real prominence in the last few decades.[21] Because of their high per unit costs, and lack of robust efficacy trials, orphan drugs are often not able to meet assessment criteria of cost-effectiveness or evidence of effectiveness.[22,23] Therefore, 'regular' assessment systems, designed for 'average' drugs used by 'average' patients are not a suitable solution for orphan drugs.

Different strategies have been proposed or implemented to manage access to orphan drugs.[24] In Chapter 2.2 we show that variability in utilisation across a sample of European countries appears to be not greater for orphan drugs than for other newly marketed drugs. This means that heterogeneity in use may not be larger for orphan drugs than for non-orphan drugs. However, we want to call for future studies that look at access to drugs at the patient level to study this topic in more detail. Furthermore, 'access' should not be treated as a binary state with a drug being either accessible or not accessible, but on a continuous scale, where actual utilisation by individual patients is the outcome.

The issue of expensive or therapeutically targeted drugs also plays role at the international level. In Chapter 2.3 we illustrate this with the example of orphan drugs and their commonalities with regard to the WHO Essential Medicines programme. The WHO Essential Medicines programme aims to stimulate the provision of medicines that meet the priority health care needs of the

population.[25] The Essential Medicines List, which is produced by the programme, has been around now for 30 years, and has played an important role in stimulating access to medicines for patients worldwide.[26] At this moment orphan drugs are not explicitly included in WHO policy, while at the same time inconsistencies exist with regard to the in- or exclusion of some orphan drugs on the Essential Medicines List. In the study in Chapter 2.3 we propose an Orphan Medicines Model List with accompanying selection criteria to bring assessment criteria in line with the therapeutic properties of drugs. After this study was published, the Committee on the Selection and Use of Essential Medicines considered the arguments brought forward in the paper, but decided to maintain the standing policy.[27] This notion may be in contrast with WHO taking a leading role in the global discussion about the provision of orphan drugs to patients who need them.

Effects of policy (interventions) on the use of drugs in clinical practice (*Section 2*)

The next section in the post-innovation learning cycle relates to the relationship between regulations in a health system and drug use in clinical practice. One of the foremost topics here are the interventions to regulate the demand side of the pharmaceutical market, such as reimbursement restrictions, co-payments and clinical guidelines. In general, we can use several study designs to assess the impact of policy interventions on drug usage in clinical practice, for example: randomised controlled trials, cross-sectional or longitudinal studies, evaluations at the aggregate or the patient level, and single or multi-country studies. Several of these designs are used in this thesis.

Cross-sectional and longitudinal studies. This thesis contains an example of a cross-sectional as well as a longitudinal study. In Chapter 3.3 we assess the association between policy interventions and actual drug usage at one moment in time. In that chapter we compare antihypertensive use in 2003 across a number of countries. Although such studies can be useful for describing broad trends and answering relatively nonspecific questions, when possible researchers should resort to longitudinal analyses, especially when the policy landscape changes at a discrete moment in time. An example of a longitudinal study, in which we compare drug use in several countries, can be found in Chapter 3.2. Here we explore the variation in use over time of a single drug with a central EU market

authorisation, clopidogrel (Plavix®). In this chapter we demonstrate how a segmentation algorithm can help in analysing the longitudinal data and in evaluating the impact of critical events and interventions. One of the drawbacks of the methods used in this chapter is that a certain amount of follow-up is needed for the algorithm to function, making it less useful for longitudinal studies that want to rapidly monitor the impact of certain events. For rapid monitoring, a method comparable to the one used in Chapter 3.1 could be used. In this study on the impact of a reimbursement restriction on the use of oral contraceptives, we track the effects of the policy intervention on discontinuation rates over time and we find that in longitudinal evaluations of policy interventions the moment in time when an assessment is made should be chosen with care.

Aggregate level and patient level studies. Another distinction that can be made is whether policy evaluations are made at the patient or at an aggregate level. Aggregate studies are a fairly straightforward and powerful method to get insight into patterns of drug use at a meso or macro level. In the study on the relationship between antihypertensive use and guideline preferences in Chapter 3.3 an aggregate method clearly shows a separation between that what is recommended in guidelines and actual use in clinical practice. However, when policy effects are restricted to certain subpopulations of patients, or cannot be captured by looking at aggregate data, this method is insufficient and more detailed analyses are required. An example of an evaluation at the patient level can be found in Chapter 3.1 where we study the impact of a reimbursement restriction on females using oral contraceptives. In this study, we found strong variation in the impact of the policy interventions between age groups; these patterns could not have been detected with a study at the aggregate level. Finally, in some situations it may be useful to include the influence of regulatory variability at different levels and the impact of different actors. For example, hospital or other regional policies can have a significant impact on drug prescribing and usage.[28]

Single and multi-country studies. The different types of studies described above can be conducted in a single or multi-country setting. In Europe the comparative study of drug usage in different countries has a long and rich tradition.[29] Since the 1970s many advances have been made in the methods used and the data sources available. A large number of studies have shown significant variability of utilisation for a wide variety of drug classes.[30,31] This tradition has created a

potentially rich and fertile landscape for conducting comparative studies of policy environments and interventions, hereby providing unique opportunities to identify 'best practices'. Our study on the use of clopidogrel, a drug with a harmonised EU market authorisation, provides an example of such a multi-country analysis.

The need for pre-planned policy evaluations

Currently, monitoring the effects of policies directed to usage of medicinal products in clinical practice is not common practice. The lack of evaluations of policy intervention was underlined in a recent Cochrane Review, which stated that: "Because pharmaceutical policies have uncertain effects and they might cause harm as well as benefits, it is important that they are properly evaluated. Evaluations should be planned ahead of introducing the policies and should be a routine part of the policy process".[32] The lack of such evaluations leads to suboptimal evidence playing an important role in the debate. To take the Dutch debate surrounding the discontinuation of the reimbursement of oral contraceptives described in this thesis as an example: prior analyses related to this intervention were done at a highly aggregated level (not looking at individual patients), were based on interviews with a small number of patients, or focused on outcomes that have a complicated causal relationship to the discontinuation of oral contraceptive reimbursement, such as the number of abortions or unplanned pregnancies.[33] In this way, debates about whether or not certain drug classes should be reimbursed are easily politicised with the role of proper clinical evidence receding to the background. In the end, the reimbursement restriction for oral contraceptives was recalled on 1 January 2008 after the political parties forming a new Dutch government agreed upon this in 2007. This decision was made without a proper evaluation of the impact of the policy measure. Based on this, we want to argue for the inclusion of rigorous (pharmaco)epidemiological analyses whenever new policy measures related to pharmaceuticals, that can influence drug use by patients, are implemented. In many cases, the resources for a detailed study at the patient level may not be available, but less advanced designs can also add significantly to the quality of the debate and decision making surrounding pharmaceutical policies.

Very few analyses of drug usage in the context of the regulatory and policy environment are conducted at the European level. In Chapter 3.2 we found a

strong disconnect between the bureaucratic reality at the community level and the clinical reality in the individual EU Member States for the therapeutic indications for clopidogrel. In particular, large international variability was observed with regard to the use of clopidogrel after stent placement. Of course, according to the 'subsidiarity principle', each EU Member State is entitled to decide on the optimal allocation of resources within its health system. However, we believe that possibly unwanted discrepancies exist between Member States when it comes to indications that are not part of the Summary of Product Characteristics (SmPC) but are reimbursed at the national level, technically constituting off-label use.[34] We believe that this should be the topic of future studies and discussions.

The use of case studies as a tool to study the relationship between the regulatory and the usage environment was applied to pharmacovigilance in Chapter 3.4. There, we propose a life-cycle model for case studies of the interaction between regulators and the various key actors in the market place in safety issue. The life-cycle model used in these case studies was developed by Snelders and Pieters.[35] With case studies such as these, we want to disentangle the role of individual actors in the discussion about a drug safety case. Furthermore, this study also showed that the discussions about drug safety should be interpreted in the context of historical and societal developments.

Pharmacoepidemiology as a learning device in pharmaceutical innovation (*Section 3*)

The third section of the cycle focuses on how drug usage in clinical practice can provide leads for drug innovation. Vandenbroucke contrasted a hierarchy of study designs focusing on 'discovery and explanation' to a hierarchy focusing on 'evaluation'.[36] In the 'discovery and explanation' hierarchy, study designs are ranked according to their ability to discover and study new explanations; anecdotal evidence and retrospective studies score high in this category. In the 'evaluation' category designs are ranked according to suitability to explore the intended effects of therapies, with randomised trials as the primary study design. In his paper, Vandenbroucke argues for science to make the best use of both worlds by using the ability to generate and test new ideas of the study designs best adapted for 'discovery and explanation', while at same time calling for the use of the evaluation designs with their confirming power when more definitive

evidence is needed. The two studies in Chapter 4 show how pharmaco-epidemiology can help to shape and focus future 'evaluation' studies. Both studies in this chapter assess the possible beneficial effects of the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the treatment of psychiatric disorders. Chapter 4.1 focuses on the possible beneficial effects of cyclooxygenase-2 COX-2 inhibitors in the treatment of schizophrenia. In Chapter 4.2 we discuss the putative positive effects of NSAIDs, in particular acetylsalicylic acid, on bipolar disorder

The study on the role of COX-2 inhibitors in treating patients with schizophrenia was based on preliminary evidence from small clinical trials.[37,38] To determine whether the detected effects were reproducible in an ambulatory population of patients using antipsychotic drugs we conducted a case-control study. The outcomes in this study were a number of medication events that were linked to disease deterioration. We were not able to show a decreased risk for disease deterioration in patients using COX-2 inhibitors. Reasons for not finding an effect in this study could be the characteristics of the study population, which was relatively old, or that the effect of COX-2 inhibitors is relatively small, as it was in the initial trials.

In contrast to the first study, the rationale for conducting the study on bipolar disorder (Chapter 4.2) was based on (neuro)pharmacological studies in animals and post-mortem analyses of brains of patients with bipolar disorder.[39] In this study we, again, chose changes in drug use as a marker for disease deterioration. To evaluate the association between the use of NSAIDs and disease deterioration in bipolar disorder, we used a study in which we compared incidence densities for the number of events between groups. Our results tentatively support the hypothesis that drugs that inhibit phospholipase A2 (PLA2) and/or COX enzymes of the arachidonic acid (AA) cascade could ameliorate the symptoms of bipolar disorder. However, future studies on this topic should be based on larger cohorts with more detailed information about the diagnosis and clinical course of disease.

The potential for such observational studies in the field of psychiatry, the focus of both studies in Chapter 4, may be empowered by developing measures for disease improvement and health status that would be applicable in observational settings and which could be related to outcome measures used in clinical trials (e.g. for depression or schizophrenia). Although we agree that defining such

measures will be very challenging, the benefits that can be reaped due to the flexibility of observational studies and the richness of available data sources warrant such an investment.

Furthermore, the studies described above were conducted with a focus on drug classes that contain either mostly off-patent drugs (the NSAIDs) or drugs for which safety concerns make other prospective studies difficult (the COX-2 inhibitors), thus providing a challenge with regard to funding and maintaining investments in knowledge creation.

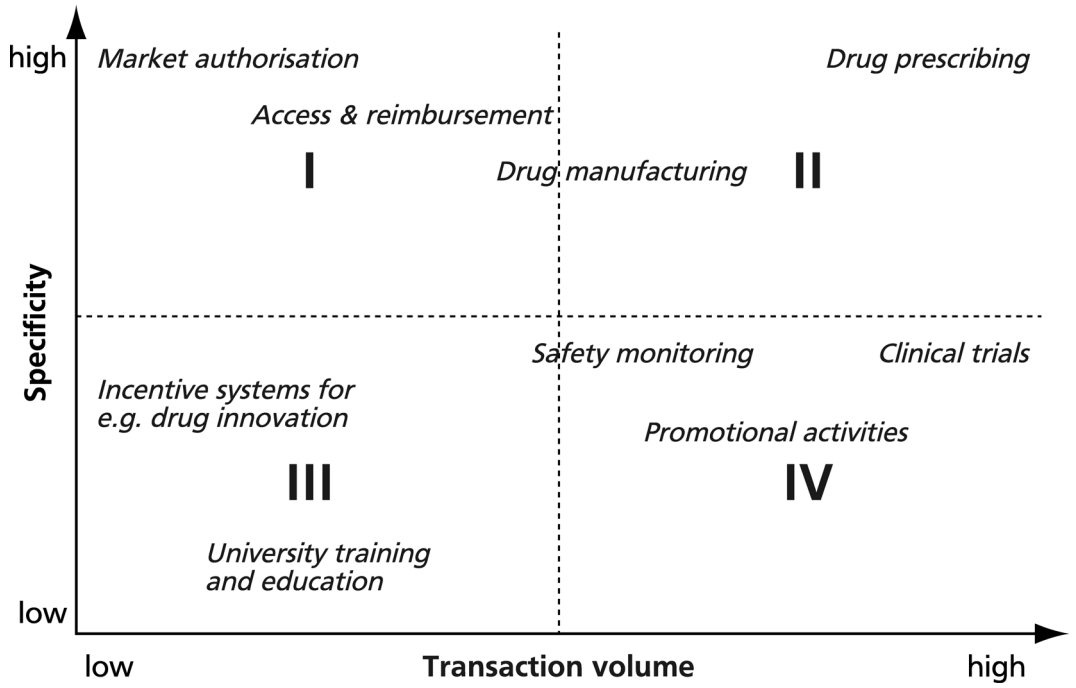
RECOMMENDATIONS FOR EVALUATING POLICIES

The post-innovation learning cycle for pharmaceuticals encompasses a wide variety of different types of rules and regulations. In this section we want to take a closer look at the types of (regulatory) environments that are encountered during the post-innovation learning cycle, and make an attempt to categorise them. As a tool for this we want to introduce a framework based on the work of the American political scientist Francis Fukuyama.[40] The original goal of Fukuyama's framework was to illustrate the challenges in measuring the output of public sector organisations. Here, we want to adapt this framework to classify different dimensions of studying pharmaceutical policy making.

The basic idea behind the framework is that activities by regulators related to pharmaceuticals can be 'scored' on two dimensions: 'specificity' and 'transaction volume'. Specificity is defined as 'the ease with which output can be measured'. Transaction volume refers to the number of decisions made in a given period of time. Based on this categorisation, a matrix with four quadrants can be constructed (Figure 2). The items that are easiest to monitor are those with a high specificity and a low transaction volume (Quadrant I). These are activities that do not occur frequently, but for which it is fairly easy to measure the final outcome of the process. A good example would be market authorisations by FDA and the European equivalent. The most complicated activities to monitor and evaluate would be those that fall in Quadrant IV. These are activities with a very high rate of events occurring while at the same time the impact of these events is hard to measure. Promotional activities by pharmaceutical companies would be a good example of this category. The activities in Quadrant II and III

form an intermediate category between Quadrant I and IV. In Quadrant II we find such activities as monitoring of drug prescribing in clinical practice, which has a very high transaction volume, but also a high specificity. To assess these activities, significant investments in databases and tools for analysis are needed. Quadrant III contains items with a low specificity and a low transaction volume. This includes for instance university education of doctors and pharmacists and the incentive systems designed to stimulate innovation. In general, the effects of these policies are very hard to measure and to quantify.

FIGURE 2 - Four quadrants for categorising (regulatory) environments related to pharmaceuticals



Based on our studies in this thesis we would like to make some specific recommendations for the different types of research questions that may come up related to the topics in this framework. The recommendations can be linked to each of the four quadrants in the framework. Below we will describe three recommendations that are common to more than one of the quadrants.

Create platforms for international information exchange of existing data (Quadrant I and II)

For many of the items that are located in Quadrant I and II, data are routinely collected. However, when studying the impact of regulations or policy interventions, especially at the international level, one of the main obstacles is retrieving good quality data. Although there are several partial datasets [41] and numerous individual projects and reports that provide snapshots of the regulatory environment at certain moments in time, making such datasets sustainable and robust has been proven difficult. Therefore, initiatives such as the Pharmaceutical Pricing and Reimbursement Information (PPRI) project supported by the Austrian government, WHO-Europe and the European Commission are very important.[42] Although setting up such a platform involves some initial costs, and requires significant continuous funding, these databases could be very helpful for regulators, patients and health professionals, as well as for researchers studying the policy environment across the EU. This was also underlined in a June 2007 European Commission report which concluded that the "rapidly changing regulatory environment makes it difficult to assess the impact of policies on expected goals, or even to obtain an up-to-date picture of the EU's regulatory landscape".[43] The same report considered that "it might…. be interesting to consider adopting a more long-term approach, exchanging evidence on a greater number of practices among national authorities". We would like to support this statement.

For pharmacoepidemiological studies, individual patient based datasets are often available at local or country levels. When these sets would be combined or compared for multiple countries, studies on the differential uptake of drugs or the effects of policy interventions from a multi-country perspective could be conducted. Such studies could help in identifying effective, but also harmful, policies. Especially in the European Union where regulations have been harmonised to a significant extent and where, in essence, 27 natural experiments can be observed, such an approach would provide an ideal learning environment. Besides the differences, we also have to look for commonalities between policy environments. For example, a large database study comparing persistence of antihypertensive medication in the USA, Canada and the Netherlands showed 180 days and 6 year persistence to be remarkably comparable, despite the health systems being vastly different.[44] Findings such as this one make fundamental

contributions to persistence research in general by looking for commonalities in radically different policy environments.

Create new data collections for low specificity activities (Quadrant III and IV)

Especially for the items in Quadrant III and IV, data collections containing information on low specificity activities are lacking. Therefore, we would like to argue for setting up large data platforms combining information from regulatory, scientific, and utilisation sources to study the incentive systems for innovation and the drug development process in general. At this moment, such studies are often conducted on an ad hoc basis, which means that much unneeded duplication takes place and many resources remain untapped.

To take one example, variations in the European Medicines Agency (EMEA) market authorisation, in particular type II variations that provide information on how scientific and technical developments diffuse into the regulatory arena, are rarely studied. A literature search in PUBMED on this topic resulted in only one study.[45] We believe that by connecting data about drug development from different sources, a rich data platform can be created. This could provide information on how innovation processes operate, as well as help in identifying 'best practices'. It could also assist in delineating the role for regulators in stimulating innovation.

Continue to expand the use of quantitative methods for policy assessment (Quadrant I and III)

One of the great challenges of studying topics with a low transaction volume is how to make the most of the relatively few data points that are generally available. Therefore, we want to argue for the development and expansion of the use of quantitative methods to study the topics that are part of this group.

For example, quantitative methods can be of enormous added value to study the various incentive systems that have been set up to stimulate innovation. In recent years, some studies have looked at the association between certain company characteristics and orphan drug development [46] or have evaluated the impact of Orphan Drug legislation using econometric methods.[47] Although such studies are an important first step, these kinds of incentive systems should also be evaluated in more detail by looking at how the different elements of the incentives influenced the drug development process. An example can be found in a recent

report from the Fraunhofer Institute that combined a wide variety of qualitative and quantitative methods to make an assessment of the European pharmacovigilance system.[48] We would alike to argue for applying these kinds of analyses to other initiatives that aim to stimulate pharmaceutical innovation, such as the Dutch Top Insititue Pharma (TI Pharma) and the EU Innovative Medicines Initiative (IMI), which both aim to give a strong impetus to the development of drugs that are important for the well-being of society.[49] Liaising with such programmes could help pharmaceutical innovation and evidence based policy making.

FINAL REMARKS ABOUT THE PRESENTED FRAMEWORK

An overarching theme of the framework presented here is that one has to consider the wide variety of topics that have to be addressed in analysing pharmaceutical policies. Each of these topics has its own features, and challenges (e.g. related to specificity and transaction volume). In this thesis we have shown how some questions that result from the post-innovation learning cycle can be answered by using methods from, for example, epidemiology. However, in many cases, answering these questions requires input from a variety of scientific disciplines and fields of expertise such as economics, law and the social sciences. Currently, many policy questions are answered from the perspective of only one of these disciplines. To build momentum and provide the right input for policy makers and regulators, researchers engaging in this field should take this multidisciplinary aspect into consideration and work towards including a wide variety of inputs. Only by providing a viewpoint encompassing insights from diverse fields of science can real evidence based health systems be designed and meaningful change achieved.

CONCLUSION

In conclusion, this thesis captures a wide variety of tools that can be applied to the study of the post-innovation learning cycle of pharmaceuticals. We have shown that certain epidemiological methods provide opportunities for studying the links between various aspects of the post-innovation learning cycle of

medicinal products. At the same time, we have identified critical issues that need to be addressed for these tools to fulfil their promise. We need to create new data platforms for low specificity activities and to expand the use of quantitative methods to support evidence-based for policy making. Moreover, the field of pharmaceutical policy making and evaluation requires a great diversity of disciplines, all of which should be engaged in designing new systems in which the needs of the patient and public health, now as well as in the future, are safeguarded in a fair and sustainable fashion.

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summary

The pharmaceutical arena is evolving constantly: new drugs enter the market while older ones are discontinued, clinical practice changes, health care budgets rise and fall, and public health needs are redefined. To assist in thinking about the usage environment of drugs in a comprehensive manner that includes regulation, clinical outcomes, and incentives for innovation, we propose in this thesis a conceptual learning cycle for pharmaceuticals that incorporates all these elements. In this thesis we focus on the 'post-innovation' part of the cycle that begins with the embedding of a new drug in the existing health care system, and ends with the leads for innovation that arise from use in clinical practice. The first section in the cycle is when a drug receives a market authorisation. At this moment, the new drug or drug class must be embedded in the existing regulatory and health system. For example, payers have to make a decision about whether or not the drug should be reimbursed, and professional organisations have to make a decision about the role of a drug in clinical practice.

In the second section of the cycle, the drug is taken up and used in clinical practice by patients and health professionals. During this period, more information comes available about the benefits and risks of the new drug. Use in clinical practice is heavily influenced by reimbursement policies and guidelines. Based on the position that the drug attains in clinical practice and the outcomes of drug treatment, the therapeutic needs of the population may change or leads for new indications or future drugs are discovered; both of these provide incentives for pharmaceutical research and development (section 3).

Results from studies on this learning cycle can be helpful in designing future policies, as well as in identifying opportunities for optimising drug use and the innovation process. The main objectives of this thesis was to develop a set of analytical tools to study the post-innovation learning cycle of pharmaceuticals. With these tools we aim to provide an evidence base for the formulation of policies that want to achieve a sustainable balance between providing good quality health care, stimulating the optimal allocation of scarce resources, and fostering an environment where innovation is adjusted to real public health needs.

This thesis contains nine studies divided in three chapters. Each chapter is located on a section of the post-innovation learning cycle. The first part of this thesis,

Chapter 2, is entitled "Embedding new drugs in the health system". In Chapter 2 we focused on several challenges for policymakers that arise from specific characteristics of new molecules.

An example is the Defined Daily Dose (DDD), which plays an important role in the price-setting systems of many countries. In *Chapter 2.1*, we focused on two enzymes involved in phase-I drug metabolism as markers of pharmacological variability: the CYP3A and CYP2D6 subsystems of cytochrome P450. The main aim of the study was to determine whether substrate drugs for CYP2D6 and/or CYP3A enzymes, which show high interindividual metabolic variability, are more prone to post-marketing adjustments of defined daily dose. A case-control design was used. We identified all DDD changes between 1982 and May 2004 through the website of the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology. Cases were drugs with a DDD change and controls were other drugs with unchanged DDDs. Information about metabolism pathway, introduction year, literature exposure and administration route was retrieved. We included 88 cases and 176 controls. Of the 88 cases, 51 were dosage decreases (58.0%). Overall, DDD changes were not associated with CYP2D6/CYP3A metabolism (odds ratio [OR] 1.92; 95% confidence interval [95%CI] 0.78–4.72). However, DDD decreases were associated with CYP2D6/CYP3A metabolism (OR 3.21; 95%CI 1.25–8.26). Adjusting for introduction year weakened this effect (OR 2.78; 95%CI 0.98–7.90). Our study indicates that CYP2D6 and CYP3A substrates are more likely to require a DDD decrease after granting of market authorisation. However, this effect was diminished by adjusting for period of introduction. The implication of this finding is that variability indicators, as is demonstrated in this study for CYP2D6/CYP3A metabolism, can exert their influence on a wide variety of drug measures, such as the DDD. In many drug price setting systems, the DDD of a drug is used as a basis for making price comparisons between drugs, meaning that these dosage changes can also have implications for regulation. Thus, molecular properties of a drug can be linked to drug characteristics that may influence pricing and reimbursement policies.

Another important challenge during the embedding of new drugs is how to handle drugs that are expensive and/or targeted to specific populations. For these drugs, regulators and third party payers have to strike a balance between the

needs of the individual patient and the optimal allocation of scarce resources. Orphan drugs are a group of special interest in this context because of high per unit costs and for usually not being able to fulfil the standard cost-effectiveness criteria. In *Chapter 2.2* we determined how utilisation of centrally authorised drugs varies across a selection of European Union (EU) member states. Our particular aim was to determine whether drugs that have received an orphan drug designation show a different level of variability in use than drugs without an orphan drug designation. We selected five orphan drugs and nine other drugs that were centrally authorised in the EU between 1 January 2000 and 30 November 2006 and that could also be used in the ambulatory setting. We compared utilisation of these drugs in seven European Union member states: Austria, Denmark, United Kingdom (represented by England), Finland, Portugal, The Netherlands, and Sweden. Utilisation data was expressed as DDDs per 1000 persons per year. For each drug, relative standard deviations (RSD) across countries were computed as a measure of variability in use. Per treatment costs and innovativeness for each drugs were determined. Drugs with an orphan drug designation were, in general, more expensive and had a higher innovation score than drugs without an orphan drug designation. We found no association between orphan drug designation status and variability in use across countries. Orphan drugs show no larger variability in utilisation than drugs without an orphan drug designation. Therefore, heterogeneity in use may be a feature of the drug market in the EU in general, and not restricted to one class of drugs.

As we describe in *Chapter 2.3*, the issue of expensive or therapeutically targeted drugs also plays role at the international level. Since 1977, the WHO Model List of Essential Medicines (EML), has provided advice for Member States that struggle to decide which pharmaceutical technologies should be provided to patients within their public health systems. At the same time, incentive systems have been put in place by various governments for the development of medicines for rare diseases ('orphan drugs'). With progress in pharmaceutical research (e.g. drugs targeted for narrower indications), these medicines will feature more often on future public health agendas. However, when current definitions for selecting essential medicines are applied strictly, orphan drugs cannot be part of the WHO Essential Medicines Programme, creating the risk that WHO may lose touch with this field. In our opinion WHO should explicitly include orphan drugs in

its policy by composing a complementary Orphan Medicines Model List as an addition to the EML. This complementary list of 'rare essentials' could aid policy-makers and patients in, for example, emerging countries to improve access to these drugs and stimulate relevant policies. Furthermore, inconsistencies in the current EML with regard to medicines for rare diseases can be resolved. In *Chapter 2.3*, we also propose selection criteria for an Orphan Medicines Model List that could form a departure point for future work towards an extensive WHO Orphan Medicines Programme.

The second section of this thesis, with the title "Effects of policy (interventions) on the use of drugs in clinical practice" (**Chapter 3**) focuses on the interaction between regulation and drug use. In this chapter we use cross-sectional and longitudinal designs, aggregate level and patient level studies, single and multi-country analyses, as well as case studies.

In *Chapter 3.1* we studied the impact of suspending oral contraceptive (OC) reimbursement in the Netherlands for women >21 years starting 1 January 2004. We determined discontinuation and switching patterns and the time course of the policy intervention's effects. The intervention cohort contained OC users on 1 January 2004, the control cohort users on 1 January 2003. Follow-up duration was one year. Discontinuation and switching patterns were assessed using relative risks (RR). Weekly refill fractions were calculated to determine the time course of the policy effects. Our intervention cohort contained 434 917 OC users, the control cohort 489 904 users. When we excluded patients not affected by the policy intervention (i.e. all patients younger than 20 years) discontinuation rates were 15.3% (intervention cohort) and 12.3% (control cohort) (RR 1.24; 95%CI 1.23–1.26) and increased with age. Switching to cheaper OCs was greatest in the intervention cohort, particularly in the 40-44 years group. Differences in cumulative refill fractions showed large variation over time. The OC reimbursement intervention led to a increase in the discontinuation rate of 24%. The effect increased with older age groups. Besides information about the impact of the policy intervention, this study pointed out that considering the time course of effects of policy interventions is of critical importance.

Chapter 3.2 focuses on the different national coverage and reimbursement strategies and their consequences for access to clopidogrel, a drug with a central

EU registration. Our objectives in this study were: 1) to assess whether changes in reimbursement policies in EU member states influenced clopidogrel prescribing; and 2) to determine whether clopidogrel-specific policy characteristics, general characteristics of the health system, or indicators for the amount of cardiovascular care delivered were associated with the level of clopidogrel prescribing. Data were collected in Austria, Belgium, Denmark, Germany, Hungary, Portugal, Slovenia, the Netherlands, and the United Kingdom (England). Utilisation rates were expressed as Defined Daily Doses (DDDs)/1000 persons/day. To determine whether changes in reimbursement policies influenced clopidogrel utilisation, a segmented linear regression approach was used. Clopidogrel prescribing varied widely in the studied countries, from 2.76 (The Netherlands) to 6.83 (Belgium) DDDs/1000 persons/day (March 2005). Six countries had therapeutic indication restrictions to clopidogrel use. Health system characteristics did not explain variation in clopidogrel prescribing. A disconnect was indicated in this study between the concept of a harmonised EU pharmaceuticals market and the reality in an individual member state. Although clopidogrel was centrally registered in the EU, policy measures at the national level result in different roles in clinical practice for this drug.

In *Chapter 3.3* variation in antihypertensive drug utilisation and guideline preferences between six European countries (Denmark, Finland, Germany, Norway, Sweden, The Netherlands) was investigated. Our objectives were to compare between-country variability in utilisation per class of antihypertensive agents and to assess guideline preferences in relation to actual use. Antihypertensive consumption data (2003) was retrieved. We classified antihypertensive agents using Anatomical Therapeutic Chemical (ATC)-codes: C02CA – alpha-blockers (AB), C03A – thiazide diuretics (TD), C07AB – beta-blockers (BB), C08CA – dihydropyridine calcium antagonists (CA), C09A/C09BA/C09BB – ACE-inhibitors + combinations (AI) and C09C/ C09D – angiotensin II receptor blockers + combinations (AT2). For each class, DDDs/1000 persons/day and share (%) of total antihypertensive utilisation was calculated. Per class, RSDs across countries were computed. Current hypertension guidelines were requested from national medical associations. Total antihypertensive utilisation varied considerably, ranging from 152.4 (The Netherlands) to 246.9 (Germany) DDDs/1000 persons/day. RSD was highest

for TD (106.2%) and AB (93.6%). Where guidelines advocated TDs (Norway, The Netherlands), TD utilisation was below (Norway) or just above (The Netherlands) median TD use. Guidelines recommended TD (Norway, The Netherlands), TD/BB/AI (Finland, German Physicians Association) or TD/BB/CA/AI/AT2 (Denmark, German Hypertension Society), Sweden had no recent national guideline. In conclusion, antihypertensive utilisation patterns varied largely across these six countries, in absolute and relative terms. Furthermore, guidelines seem disconnected from clinical practice in some countries, and none of the guidelines discuss current utilisation. Whether this reflects a need for change in prescribing or re-evaluation of guidelines warrants further research.

The use of case studies as a tool to study the relationship between the regulatory and the usage environment was applied to pharmacovigilance in *Chapter 3.4*. There, we propose a life-cycle model for case studies of the interaction between regulators and the various key actors in the market place in safety issue. The life-cycle model used in these case studies, a so-called Seige-cycle, was developed by Snelders and Pieters. The Seige cycle is a general abstraction of drug careers. The Seige cycle facilitates a comparative long-term perspective on the development, use and governance of various agents or classes of agents. In this study we propose the use of a Seige-cycle model to study two drug safety cases: the market withdrawal of cerivastatin (Lipobay®) and the discussion about the relationship between Selective Serotonin Re-uptake Inhibitors (SSRIs) and suicide. For both cases we describe the regulatory landscape in which the drug emerges at the moment of market authorisation, followed by the transactions between key actors that changed the regulatory landscape, and, using publication counts, we show how the debate in the scientific literature evolved. Finally, we superimpose these dynamics on the Seige-cycle. Both cases show strong variation in the roles of the key actors in the development of the safety case. Furthermore, both cases show different dynamics over time and can be placed at different points on the Seige-cycle. The Seige-cycle framework used in this study could be a useful tool to study drug safety issues in a life-cycle related context. Future studies should develop this method further and should look at ways to quantify Seige-cycle.

The final part of this thesis is "Pharmacoepidemiology as a learning device in pharmaceutical innovation" (**Chapter 4**). In Chapter 4 we present two studies from the field of psychiatry that show how information from actual use in clinical practice can provide leads for drug development. The two studies in Chapter 4 show how pharmacoepidemiology can help to shape and focus future 'evaluation' studies.

In *Chapter 4.1* we explore the reports about the possible beneficial effects of cyclooxygenase (COX)-2 inhibitors on schizophrenia. The study was based on preliminary evidence from small clinical trials. Our observational study assesses the association between exposure to COX-2i or/and non-steroidal anti-inflammatory drugs (NSAIDs) and schizophrenia deterioration. We conducted a case-control study within a cohort (n=3485) of antipsychotic users with a schizophrenia diagnosis (International Classification of Diseases, ICD-9=295.x) in IMS-Lifelink, a US claims database. Case events indicating exacerbation of schizophrenia were: switching antipsychotic medication, starting combination therapy, using parenteral antipsychotics or an increasing dose. For each case one control was selected. Exposure to COX-2 inhibitors/NSAIDs (current/recent/none) and cumulative exposure in Defined Daily Doses 90 days before the index/event date were assessed. Age, sex and co-medication were evaluated as confounders. Logistic regression analysis was used to assess the association. 1443 case events occurred. For current use, no benefit on schizophrenia case events from exposure to COX-2 inhibitors was found (adjusted OR 1.16; 95%CI 0.83-1.62). Instead, recent COX-2 inhibitor use with a duration of 0 to 93 days was associated with an increased risk for schizophrenia deterioration (adjusted OR 2.56; 95%CI 1.35-4.87). This association was strongest in rofecoxib. No relation was found for NSAIDs. The use of COX-2 inhibitors was not associated with a decreased risk for schizophrenia deterioration in this population.

The rationale for conducting the study on bipolar disorder described in *Chapter 4.2* was based on (neuro)pharmacological studies in animals and post-mortem analyses of brains of patients with bipolar disorder. Mood stabiliser administration to rats downregulates markers of brain arachidonic acid (AA) metabolism, including phospholipase A2 (PLA2) and COX. Furthermore, some evidence indicates that the AA cascade is upregulated in bipolar disorder (BD). We

hypothesise that agents targeting the AA cascade will ameliorate BD symptoms. We collected medication histories of patients who had been prescribed lithium from the PHARMO database. Data were stratified according to drug classes that inhibit PLA2 and/or COX enzymes and duration of use. Incidence density (ID) of BD medication events (dose increases/substance changes) was used as a proxy for BD deterioration. ID ratios in patients with COX and/or PLA2 inhibitors next to lithium were compared to ID ratios in patients using lithium alone. Low-dose aspirin significantly reduced the ID ratio of medication events, independent of duration of use. The ID ratio of NSAIDs and glucocorticoids was not different from 1.0 if prescribed for ≥180 or ≥90 days, but significantly exceeded 1.0 when shorter durations of use were included. Selective COX-2 inhibitors had no significant effect and multiagent administration increased the ID ratio above 1.0. These preliminary neuroepidemiological results indicate that low-dose aspirin may ameliorate symptoms of BD patients taking lithium, warranting further studies.

In **Chapter 5** we place our findings from this thesis in a broader context. This thesis captures a wide variety of tools that can be applied to the study of the post-innovation learning cycle of pharmaceuticals. We have shown that certain epidemiological methods provide opportunities for studying the links between various aspects of the post-innovation learning cycle of medicinal products. At the same time, we have identified critical issues that need to be addressed for these tools to fulfil their promise. We need to create new data platforms and to expand the use of quantitative methods to support evidence-based for policy making. Moreover, the field of pharmaceutical policy making and evaluation requires a great diversity of disciplines, all of which should be engaged in designing new systems in which the needs of the patient and public health, now as well as in the future, are safeguarded in a fair and sustainable fashion.

samenvatting

Het farmaceutische veld is voortdurend in ontwikkeling: nieuwe geneesmiddelen komen op de markt, terwijl oudere middelen verdwijnen, de klinische praktijk verandert, budgetten wijzigen en de behoeften vanuit volksgezondheids-perspectief worden hergedefinieerd. Om het denken over, en leren van de gebruiksomgeving van geneesmiddelen op een brede wijze te stimuleren stellen we in dit proefschrift een conceptuele leercyclus voor geneesmiddelen voor. In deze cyclus bevinden zich elementen als regelgeving, klinische uitkomsten en prikkels voor innovatie. In dit proefschrift richten we ons op het 'post-innovatie' gedeelte van de leercyclus. Deze begint met de inbedding van nieuwe geneesmiddelen in een bestaand zorgsysteem en eindigt met aanwijzingen voor innovatie die voortkomen uit het gebruik van geneesmiddelen in de praktijk. Het eerste deel van de cyclus bevindt zich op het moment dat een nieuw geneesmiddel toegang tot markt krijgt. Op dit moment moet het geneesmiddel ingebed worden in bestaande regelgeving en zorgprocessen. Overheid en zorgverzekeraars moeten bijvoorbeeld een keuze maken of een middel al dan niet vergoed wordt en beroepsgroepen moeten de plek van het middel in de klinische praktijk bepalen. In het tweede deel van de cyclus wordt het geneesmiddel toegepast door patiënten en zorgverleners. Gedurende deze periode komt veel nieuwe informatie beschikbaar over de risico's en baten van het nieuwe geneesmiddel. Het gebruik in deze periode wordt in sterke mate bepaald door vergoedingsbesluiten en behandelrichtlijnen. Op basis van de positie die een middel in de praktijk heeft, en de klinische uitkomsten die daarvan het resultaat zijn, veranderen mogelijk de therapeutische behoeften van de populatie en kunnen nieuwe indicaties ontdekt worden. Dit kan weer zorgen voor prikkels voor geneesmiddelonderzoek en ontwikkeling (deel 3 van de cyclus).

Het bestuderen van deze leercyclus kan behulpzaam zijn bij het ontwerpen van toekomstig beleid, alsmede bij het identificeren van kansen om optimaal geneesmiddelgebruik en innovatie te stimuleren. De belangrijkste doelstelling van dit proefschrift was om een aantal analytische instrumenten te ontwikkelen om de post-innovatie leercyclus voor geneesmiddelen te bestuderen. Met deze instrumenten willen we bijdragen aan de beschikbare evidentie voor het formuleren van beleid dat een duurzame balans beoogt tussen zorg van goede

kwaliteit, met een optimale allocatie van schaarse middelen in een omgeving waar innovatie aansluit bij de volksgezondheidsbehoeften.

Het eerste deel van dit proefschrift, **Hoofdstuk 2**, heeft als titel "Het inbedden van nieuwe geneesmiddelen in het zorgstelsel". In Hoofdstuk 2 richten we ons op verschillende uitdagingen waar beleidsmakers voor staan en die voortkomen uit de specifieke eigenschappen van nieuwe geneeskrachtige moleculen. Een voorbeeld hiervan vinden we in de 'Defined Daily Dose' (DDD), dit is een doseringsmaat die een belangrijke rol speelt bij de prijsbepaling van geneesmiddelen in verschillende landen.

In *Hoofdstuk 2.1* bestuderen we twee enzymen die betrokken zijn bij het fase-I metabolisme als marker voor farmacologische variabiliteit, te weten de CYP3A en CYP2D6 subsystemen van het cytochroom P450. Het doel van deze studie was om te bepalen of geneesmiddelen die een substraat zijn voor CYP2D6 en/of CYP3A (enzymen die sterke inter-individuele metabole variabiliteit vertonen) meer vatbaar zijn voor postmarketing aanpassingen in de DDD. We gebruikten hiervoor een case-controle opzet. We identificeerden alle DDD wijzigingen tussen 1982 en mei 2004 via de website van het Wereldgezondheidsorganisatie (WHO) Collaborating Centre for Drug Statistics Methodology. Cases waren geneesmiddelen met een DDD wijziging, controles werden geselecteerd uit alle andere geneesmiddelen zonder een DDD wijziging. Informatie over de metaboliseringsroute, jaar van introductie, aantal publicaties in de wetenschappelijke literatuur (als maat voor aandacht voor het middel) en route van toediening werd verzameld per geneesmiddel. We includeerden 88 cases en 176 controles in de studie. 51 van de 88 cases waren dosisverlagingen (58,0%). In een ongestratificeerde analyse waren DDD veranderingen niet geassocieerd met CYP2D6/CYP3A metabolisme (odds ratio [OR] 1,92; 95% betrouwbaarheids-interval [95%CI] 0,78–4,72). Echter, DDD verminderingen waren wel geassocieerd met CYP2D6/CYP3A metabolisme (OR 3,21; 95%CI 1,25–8,26). Correctie voor het jaar van introductie verzwakte dit effect (OR 2,78; 95%CI 0,98–7,90). Onze studie laat zien dat het voor substraten van CYP2D6 en CYP3A waarschijnlijker is dat ze een DDD verlaging nodig hebben na toelating tot de markt dan middelen die geen substraat voor deze enzymen zijn, hierbij in ogenschouw nemende dat dit effect werd verkleind door correctie voor het jaar

van introductie. Deze bevinding impliceert dat indicatoren voor variabiliteit, zoals in deze studie CYP2D6/CYP3A metabolisme, hun invloed uit kunnen oefenen op een groot aantal maten (zoals de DDD). In veel vergoedingssystemen wordt de DDD gebruikt als een maat om vergelijkingen te maken tussen geneesmiddelen, dit betekent dat deze dosisveranderingen ook van betekenis zijn voor regelgeving. Op deze manier kunnen moleculaire eigenschappen van een geneesmiddel invloed uitoefenen op prijs- en vergoedingsmaatregelen.

Een belangrijke uitdaging bij het inbedden van nieuwe geneesmiddelen is hoe men om gaat met geneesmiddelen die zeer duur zijn en/of bestemd voor specifieke populaties. Voor deze geneesmiddelen moeten beleidsmakers een balans vinden tussen de behoefte van de individuele patiënt en de optimale allocatie van schaarse middelen voor het systeem als geheel. Weesgeneesmiddelen zijn een groep van speciale betekenis in deze context vanwege de hoge kosten per eenheid en de soms optredende problemen bij het voldoen aan eisen voor kosten-effectiviteit. In *Hoofdstuk 2.2* bepaalden we hoe het gebruik van centraal geautoriseerde geneesmiddelen varieerde in selectie van lidstaten van de Europese Unie (EU). In het bijzonder keken we hier naar geneesmiddelen die als weesgeneesmiddel waren aangemerkt en in hoeverre de variabiliteit in gebruik afweek van dat van 'gewone' geneesmiddelen. We selecteerden vijf weesgeneesmiddelen en negen andere geneesmiddelen met een centrale marktautorisatie voor de hele EU. De marktautorisatie was verkregen tussen 1 januari 2000 en 30 november 2006. De geneesmiddelen moesten gebruikt worden buiten het ziekenhuis. We vergeleken gebruik in zeven EU lidstaten: Denemarken, Engeland, Finland, Nederland, Oostenrijk, Portugal en Zweden. Gebruik werd uitgedrukt in DDDs per 1.000 personen per jaar. Voor elk geneesmiddel werd een relatieve standaarddeviatie (RSD) berekend voor het gebruik over de landen in de studie als een maat voor variabiliteit in gebruik. Kosten per behandeling en een innovativeitsscore werden bepaald voor ieder geneesmiddel. In het algemeen waren weesgeneesmiddelen duurder en hadden een hogere innovativiteitsscore dan andere geneesmiddelen. We vonden geen associatie tussen de status als weesgeneesmiddel en variabiliteit in gebruik tussen landen. Weesgeneesmiddelen laten geen grotere variabiliteit in gebruik zien dan niet-weesgeneesmiddelen. Heterogeniteit in gebruik is mogelijk een eigenschap

van de gehele geneesmiddelenmarkt in de EU en niet beperkt tot één klasse geneesmiddelen.

Zoals we in *Hoofdstuk 2.3* laten zien speelt het onderwerp van dure geneesmiddelen die zich richten op een specifieke populatie ook in de internationale discussie een rol. Sinds 1977 stelt de WHO een zogenaamde 'Model List of Essential Medicines (EML)' samen om lidstaten te adviseren welke geneesmiddelen zij in ieder geval beschikbaar moeten maken voor hun burgers. Ondertussen zijn er wereldwijd systemen ingericht om de ontwikkeling van geneesmiddelen voor zeldzame ziekten (weesgeneesmiddelen) te stimuleren. In de toekomst zullen weesgeneesmiddelen zonder twijfel een prominente plaats op de agenda innemen. Echter, indien de huidige selectiecriteria voor de EML strikt worden toegepast, dan kunnen weesgeneesmiddelen geen onderdeel zijn van het WHO programma voor Essential Medicines. Hierdoor ontstaat het risico dat dit WHO programma het contact met het weesgeneesmiddelendossier verliest. Daarom zijn wij van mening dat de WHO weesgeneesmiddelen expliciet in zijn beleidssfeer moet incorporeren door een 'Orphan Medicines Model List' naast de EML samen te stellen. Deze complementaire lijst kan beleidsmakers in, bijvoorbeeld, opkomende economieën helpen om de toegang tot weesgeneesmiddelen te verbeteren. Bovendien kunnen bestaande inconsistenties in de EML, waar zich nu reeds weesgeneesmiddelen op bevinden, worden vermeden. In *Hoofdstuk 2.3* stellen we eveneens selectiecriteria voor die voor de 'Orphan Medicines Model List' gebruikt kunen worden.

Het tweede deel van dit proefschrift heeft de titel "De effecten van beleid (en beleidsinterventies) op geneesmiddelgebruik in de klinische praktijk" (**Hoofdstuk 3**). Dit hoofdstuk richt zich op de interactie tussen regelgeving en geneesmiddelgebruik in de praktijk. We gebruiken hiervoor crossectionele en longitudinale analyses, studies op geaggregeerd nivo en op patiëntnivo, één- en meerlandenstudies en casuïstische studies.

In *Hoofdstuk 3.1* bestuderen we de invloed van het opschorten van de vergoeding van orale anticonceptiva (OA) in Nederland voor vrouwen ouder dan 21 jaar vanaf 1 januari 2004. We bepaalden stop- en switchpatronen en het tijdsverloop van de effecten van de interventie. Het interventiecohort bevatte OA gebruikers op 1 januari 2004. Het controle cohort bestond uit OA

gebruikers op 1 januari 2003. We volgden beide groepen voor één jaar. Stop- en switchpatronen werden vergeleken met behulp van Relatieve Risico's (RR). Voor iedere week werd een 'ophaalfractie' berekend (de cumulatieve fractie van alle patiënten die in een bepaalde week was teruggekomen om, na de indexdatum, een nieuw recept voor een OA op te halen). Het interventiecohort bestond uit 434.917 OA gebruikers, het controle cohort uit 489.904 gebruikers. Indien we gebruikers excludeerden die niet door de beleidsmaatregel werden geraakt (alle vrouwen jonger dan 20 jaar) vonden we dat 15,3% van de patiënten in het interventiecohort en 12,3% van de patiënten in het controlecohort stopten met OA (RR 1,24; 95%CI 1,23–1,26). Deze percentages namen toe met de leeftijd. Switchen naar een goedkoper OA werd vooral gezien in het interventiecohort en dan met name in de groep van 40 tot 44 jaar. De verschillen in de cumulatieve ophaalfractie vertoonde een sterke variatie over de tijd. De beleidsinterventie leidde uiteindelijk tot een stijging in het percentage patiënten dat in het jaar na de indexdatum stopte met OAs van 24%, toenemend met de leeftijd. Naast deze informatie liet de studie zien dat het van groot belang is om het tijdsverloop van de effecten van de beleidsinterventie mee te nemen bij beleidsevaluaties rond geneesmiddelen.

Hoofdstuk 3.2 richt zich op de verschillen in nationale vergoedingssystemen en strategieën die in EU lidstaten gekozen worden en hun invloed op de toegang tot clopidogrel, een geneesmiddel met een centrale marktautorisatie voor de hele EU. Ons doel in deze studie was om: 1) te bepalen of wijzigingen in het vergoedingsbeleid in EU lidstaten het gebruik van clopidogrel beïnvloedde; en 2) te bepalen of voor clopidogrel specifieke beleidskenmerken, algemene karakteristieken van het zorgstelsel, of indicatoren voor de hoeveelheid geleverde cardiovasculaire zorg geassocieerd waren met de omvang van het gebruik van clopidogrel in een land. Data werden verzameld in België, Denemarken, Duitsland, Engeland, Hongarije, Nederland, Oostenrijk, Portugal en Slovenië. Gebruik werd uitgedrukt als aantal DDDs per 1.000 personen per dag. Om te bepalen of veranderingen in het vergoedingsbeleid het gebruik van clopidogrel beïnvloedden gebruikten we een gesegmenteerde lineaire regressie benadering. Clopidogrel gebruik varieerde sterk tussen de landen in de studie: van 2,76 (Nederland) tot 6,83 (België) DDDs/1.000 personen/dag in maart 2005. Zes landen in de studie hadden therapeutische restricties voor wat betreft het gebruik

van clopidogrel. Algemene karakteristieken van het zorgstelsel verklaarden het verschil in clopidogrel gebruik niet. Deze studie liet een hiaat ziet tussen de idee van een geharmoniseerde markt voor geneesmiddelen in de EU en de realiteit in de afzonderlijke lidstaten. Hoewel clopidogrel centraal geregistreerd was in de EU, leidden nationale beleidsregels tot radicaal verschillende posities voor dit geneesmiddel in de klinische praktijk.

In *Hoofdstuk 3.3*. onderzochten we de variatie in het gebruik van antihypertensiva en voorkeuren in richtlijnen in zes Europee landen (Denemarken, Duitsland, Finland, Nederland, Noorwegen en Zweden). Ons doel in deze studie was om de variabiliteit in het gebruik van antihypertensiva tussen landen te vergelijken en om de relatie tussen voorkeuren in behandelrichtlijnen te vergelijken met daadwerkelijk gebruik in de klinische praktijk. We verzamelden gebruiksgegevens voor antihypertensiva voor het jaar 2003. We verdeelden de geneesmiddelen in zes groepen op basis van ATC-codes: C02CA – alfa-blokkers (AB), C03A – thiazide diuretica (TD), C07AB – beta-blokkers (BB), C08CA – dihydropyridine calcium antagonisten (CA), C09A/C09BA/C09BB – ACE-inhibitoren + combinaties (AI) en C09C/C09D – angiotensine II receptor blockers + combinaties (AT2). Voor elke groep werd het gebruik in DDDs per 1.000 personen per dag berekend, alsmede het % van het totale antihypertensiva gebruik. Per groep werden relatieve standaarddeviaties over de geïncludeerde landen berekend. Huidig behandelrichtlijnen werden opgevraagd bij nationale medische beroepsverenigingen. Het totale antihypertensivagebruik varieerde in ruime mate, van 152,4 DDDs/1.000 personen/dag in Nederland tot 246,9 DDDs/1.000 personen/dag in Duitsland. De RSD was het hoogste voor TD (106,2%) en AB (93,6%). Waar richtlijnen TDs adviseerden (Noorwegen en Nederland) was het TD gebruik onder (Noorwegen) of net boven (Nederland) het mediane TD gebruik. Behandelrichtijnen raadden aan: TD (Noorwegen, Nederland), TD/BB/AI (Finland, Duitse Artsenvereniging) of TD/BB/CA/AI/AT2 (Denemarken, Duits Hypertensie Genootschap), Zweden had geen recente nationale richtlijn. Geconcludeerd kan worden dat het gebruikspatroon van antihypertensiva sterk verschilde tussen de zes landen, zowel in absolute als in relatieve zin. In sommige landen lijkt zich een kloof te bevinden tussen wat behandelrichtlijnen aanraden en wat in de praktijk gebruikelijk is. Geen van de behandelrichtlijnen bespreekt het huidige gebruikspatroon van antihypertensiva.

Of dit een noodzaak voor verandering in voorschrijfgedrag of in het formuleren van behandelrichtlijnen impliceert zal toekomstig onderzoek moeten uitwijzen.

In *Hoofdstuk 3.4* trachten we met behulp van een casuïstische benadering licht te werpen op de relatie tussen regelgeving en gebruik bij farmacovigilantie. In dit hoofdstuk stellen we een levenscyclus model voor geneesmiddelen voor om de interactie tussen regulerende instanties en de verschillende sleutelpartijen te bestuderen. Het levenscyclus model dat in deze casusstudies wordt gebruikt is ontwikkeld door Snelders en Pieters: de zogenaamde Seige-cyclus. De Seige-cyclus is een abstractie van de carrières van geneesmiddelen. De Seige-cyclus faciliteert een lange-termijn perspectief op de ontwikkeling, het gebruik en de regulering van geneesmiddelen. In dit hoofdstuk passen we de Seige-cyclus toe op twee veiligheidscasus: het van de markt halen van cerivastatine (Lipobay®) en de discussie rond de relatie tussen Selectieve Serotine heropnameremmers (SSRIs) en zelfmoord. Voor beide casus beschrijven we het 'landschap' waarin het middel op de markt komt, gevolgd door een beschrijving van de 'transacties' tussen de verschillende sleutelspelers, en, gebruikmakend van tellingen van het aantal wetenschappelijke publicaties, laten we zien hoe het debat zich in de literatuur ontwikkelt. Vervolgens bespreken we deze ontwikkelingen in het kader van de Seige-cyclus. Beide casus laten een verschillende rol van de sleutelspelers zien gedurende de casus. Bovendien kunnen de twee casus op verschillende punten van de Seige-cyclus geplaatst worden. Het kader van de Seige-cyclus, zoals in deze studie gebruikt, kan een nuttige rol vervullen bij het bestuderen van veiligheidsvragen. Toekomstige studies zullen deze methodologie verder uit moeten werken en zich met name richten op de wijze hoe de Seige-cyclus verder beschreven en gekwantificeerd kan worden.

Het laatste deel van dit proefschrift is getiteld "Farmacoepidemiologie als een hulpmiddel in farmaceutische innovatie" (**Hoofdstuk 4**). In dit hoofdstuk laten twee studies in een psychiatrische setting zien die tonen hoe informatie uit de gebruiksomgeving aanwijzingen voor geneesmiddelontwikkeling kan geven. De twee studies in Hoofdstuk 4 tonen hoe farmacoepidemiologie kan helpen om toekomstige (klinische) studies vorm te geven.

In *Hoofdstuk 4.1* bestuderen we de mogelijke positieve effecten van cyclooxygenase-2 inhibitors (COX2i) bij schizofrenie. Deze studie was gebaseerd

op bevindingen uit kleine klinische trials. In onze observationele studie onderzochten we de associatie tussen blootstelling aan COX2i en/of NSAIDs en de verslechtering van schizofrenie. We voerden een case-controle studie uit in een cohort (n=3.485) van antipsychoticagebruikers met een schizofrenie diagnose (International Classification of Diseases, ICD-9=295.x) in de IMS-Lifelink database. Case events die een verslechtering van schizofrenie indiceerden waren: switchen van antipsychoticamedicatie, het starten met combinatietherapie, het gebruik van parenterale antipsychotica of een stijging in de dagelijkse dosis. Voor elke case werd één controle geselecteerd. Blootstelling aan COX-2i/NSAIDs (huidig/recent/geen) en cumulatieve blootstelling in DDDs 90 dagen voor de indexdatum werden bepaald. Leeftijd, geslacht en comedicatie werden geïncludeerd als mogelijke confounders. We gebruikten logistische regressie analyse om de associaties te onderzoeken. Voor huidig gebruik vonden we geen positief effect op het aantal case events door blootstelling aan COX-2i. (gecorrigeerde OR 1,16; 95%CI 0,83-1,62). In tegendeel, recent COX-2i gebruik met een duur van 0 tot 93 dagen was geassocieerd met een verhoogd risico voor verslechtering van schizofrenie (gecorrigeerde OR 2,56; 95%CI 1,35-4,87). De associatie was het sterkst voor rofecoxib. Geen relatie werd gevonden voor de NSAIDs. Het gebruik van COX-2i was niet geassocieerd met een verlaagd risico voor de verslechtering van schizofrenie in deze populatie.

De reden voor het uitvoeren van de studie in *Hoofdstuk 4.2* waren (neuro)farmacologische studies in dieren en post-mortem onderzoek van de hersenen van patiënten met bipolaire stemmingsstoornissen (BD). De toediening van stemmingsstabilisatoren aan ratten downreguleert markers voor arachidonzuur (AA) in de hersenen, waaronder fosfolipase A2 (PLA2) en COX. Er zijn ook aanwijzingen dat de AA cascade is ge-upreguleerd in patienten met bipolaire stemmingsstoornissen. Onze hypothese in deze studie is dat stoffen die aangrijpen op de AA cascade de symptomen van bipolaire stemmingsstoornissen verbeteren. We verzamelden medicatiehistorie van patiënten die lithium voorgeschreven hadden gekregen uit de PHARMO database. Data werden gestratificeerd naar geneesmiddelklassen die PLA2 en/of COX-2 enzymen remmen en naar duur van gebruik. De incidentiedichtheid (ID) van BD medicatie events (dosis verhoging of veranderde actieve substantie) werd gebruikt als maat voor BD verslechtering. ID ratio's in patiënten met COX en/of PLA2

inhibitors naast lithium werden vergeleken met ID ratio's in patiënten die alleen lithium gebruikten. Lage dosis aspirine reduceerde de ID ratio voor medicatie events significant, onafhankelijk van de duur van gebruik. De ID ratio voor NSAIDs en glucocorticoïden week niet significant af van 1,0 wanneer het werd voorgeschreven voor meer dan 180 of meer dan 90 dagen, maar week wel statistisch significant af van 1,0 wanneer korte gebruiksduren in de analyse werden geïncludeerd. Selectieve COX-2i hadden geen significant effect en het toedienen van meerdere middelen deed het ID ratio boven 1,0 stijgen. Deze voorlopige neuroepidemiologische resultaten laten zien dat lage dosis aspirine mogelijk de symptomen van BD verbetert in patiënten die lithium gebruiken.

In **Hoofdstuk 5** plaatsen we onze bevindingen in een bredere context. Dit proefschrift bevat een variëteit aan instrumenten die gebruikt kunnen worden om de post-innovatie leercyclus van geneesmiddelen te bestuderen. We hebben laten zien dat bepaalde epidemiologische methoden de verbindingen tussen de verschillende delen in de post-innovatie leercyclus kunnen helpen begrijpen. Tegelijkertijd hebben we enkele kritische zaken geïdentificeerd waaraan aandacht geschonken moet worden. Zo is er behoefte aan nieuwe dataplatforms, moet het gebruik van kwantitatieve methodes worden uitgebreid en moet een multidisciplinaire aanpak gekozen worden. Alleen op deze manier kunnen nieuwe systemen in de gezondheidszorg ontworpen worden die, nu en in de toekomst, in de behoeften van patiënten en het zorgstelsel als geheel op een duurzame wijze kunnen voorzien.

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Op deze plaats wil ik een aantal mensen bedanken die gedurende mijn werkzaamheden aan de Universiteit Utrecht een inhoudelijke bijdrage hebben geleverd aan de totstandkoming van dit proefschrift.

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Naast mijn promotor en co-promotor zijn er natuurlijk nog vele anderen die vanuit de Disciplinegroep Farmacoepidemiologie en Farmacotherapie inhoudelijke ondersteuning hebben gegeven. In het bijzonder wil ik Patrick Souverein en Svetlana Belitser bedanken voor hun hulp bij de verschillende netelige problemen die soms opdoemen bij het bewerken of analyseren van datasets. En, uiteraard mogen de dames van het secretariaat niet vergeten worden voor hun immer wijze raad en daad.

In several studies in this thesis we made use of data from different European countries. For these studies, the 'PILLs network' was created. This network consists of scientists from various EU Member states who found time in their busy schedules to assist us with locating and retrieving the right data. Without

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list of publications

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Pieter Stolk was born in Rotterdam, The Netherlands on August 21st, 1978. In 1996 he graduated from the Erasmiaans Gymnasium in Rotterdam and started his studies in Pharmacy at Utrecht University. In 2002 he obtained his 'doctorandus' degree, followed by his PharmD in 2003. During his studies he completed a research traineeship at the Faculty of Pharmacy of the University of Toronto, Canada.

This thesis was written while working as a PhD student at the Division of Pharmacoepidemiology and Pharmacotherapy, Department of Pharmaceutical Sciences, Faculty of Science of Utrecht University. The studies presented in this thesis were conducted under the supervision of Prof. dr. H.G.M. Leufkens and Dr. E.R. Heerdink.

During his work at the Division of Pharmacoepidemiology and Pharmacotherapy, he was one of the course directors for the Utrecht Summer School on Pharmaceutical Policy Analysis 2007. He was also part of the organising committee for the Conference on Pharmaceutical Policy Analysis, a three-day international conference that was held in September 2007 in Zeist, The Netherlands. Furthermore, he was involved in setting up the WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceutical Policy Analysis.