

# CROSS-COUNTRY VARIATION IN MEDICINES USE

## A pharmaceutical system perspective

**Joëlle Hoebert**

The research presented in this PhD thesis was conducted under the umbrella of the Utrecht World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation, which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands. The Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence-based policy analysis and conceptual innovation in the area of policy making and evaluation in general.

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# CROSS-COUNTRY VARIATION IN MEDICINES USE

## A pharmaceutical system perspective

Variatie in geneesmiddelengebruik tussen landen  
Een systeembenadering  
(met een samenvatting in het Nederlands)

Proefschrift

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# CHAPTER 1

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GENERAL INTRODUCTION





## INTRODUCTION

Access to effective and affordable medicines (medical care) is considered an equitable right for all (European) citizens [1]. However, ensuring access to medical care is a challenge for governments and pharmaceutical systems across the world. The shift in the demographics of most European countries, as people age and require more medical care, in combination with national budgets that are strained to their limits, poses a serious challenge to society [2]. The fact that newly developed medicines are generally rather costly complicates the situation even further. For example, proper and affordable health care is seen as a priority for many governments, but at the same time governments should also support a viable (national) pharmaceutical industry [3]. Over the past years, it has become obvious that governments must make a choice between patients' needs and an optimal allocation of resources. Or, quoting the noted economist Milton Friedman, 'there is no such thing as a free lunch' [4].

A national health care system includes organizations and decisions deliberately constructed to provide for the health needs of individuals, groups, communities, and the wider society. Thus, a family may belong to a health system that includes a physician, health practices and the decisions of its members. The European Union (EU) has created a health care system that includes the European Medicines Agency (EMA) that shares responsibility for a centralised registration process for new medicines. Between a family and the EU health systems are national, regional, state and local health systems in each country [5]. The behaviour of the population and pharmaceutical policies are two key components of any health care system. Without strong policies, a system may not function properly, and may not make the most efficient use of its resources [6,7].

Health care systems and as part of that the pharmaceutical care systems stem from specific political, historical, cultural and socio-economic traditions. As a result, the organisational arrangements for health care differ considerably among EU member states—as do capital and human resource allocation [8]. Policy makers across European countries may make distinct decisions to guarantee their population (affordable) access to medicines. Physicians make patient-specific decisions in their choice between treatment options and patients often vary in their treatment-seeking decisions. As a result, variation in the uptake and level of medicines use is a natural consequence of each EU country's system.

This thesis aims to gain insight into the cross-national variation in medicines use in the EU. The level of medicines use in multiple countries and across several medical conditions is measured, and an analysis is presented of various pharmaceutical system factors that explain possible cross-national variation in medicines use.

### **Existing examples of cross-national variation in medicines use and parameters of pharmaceutical systems**

The following examples are illustrations of cross-national variation in medicines use in the EU. Most studies focused on cross-national variation in medicines use, thereby identifying possible explanations for the observed variation. Other studies did not include the level of medicines use in their analysis, but focused explicitly on the variation in pharmaceutical system factors, such as pharmaceutical policies (possibly) leading to cross-national variation in medicines use.

Cars et al. (2001) for instance, showed a wide variation in outpatient antibiotic use among EU countries, see figure 1 [9]. This variation is unlikely to be caused by differences in the frequency of bacterial infections. The pronounced difference between Belgium and the Netherlands is noteworthy because of the close proximity of the two countries and their common language. The authors concluded that the attitudes of physicians and patients to antibiotics, historical backgrounds, cultural and social factors, and disparities in health care systems were also important factors in determining the observed antibiotic prescribing patterns. The importance of cultural diversity in antibiotic prescribing was supported in a study of DeSchepper et al. (2008). This study identified several cultural aspects associated with antibiotic use, such as the relationship between health care professionals and patients, as well as the relationship between professionals [10]. Cross-national variation and cultural diversity for another therapeutic class of medicines was also reported by Bhatt et al. (2005). They found substantial international variation in patients' medication use by physicians' specialty, whereby the prescription frequency for statins by cardiologists was (significantly) higher than those for other physician specialties, thus highlighting the differences in professional attitudes to treatment as a potentially important factor underlying the international variation of medicines use [11].

Pharmaceutical care systems have become more sophisticated in recent years to accommodate patient demand and higher prices for new and effective medicines, such as biologicals. In trying to explain the variation observed in the uptake of Tumour Necrosis Factor alpha (TNF alpha) inhibitors, Jönsson et al. (2008) noted differences in national income (as measured by gross domestic product (GDP)) as an important reason for the lower use of medicines in the countries of central and eastern Europe compared with western Europe [12]. However, there were also considerable differences between countries with broadly the same GDP, possibly

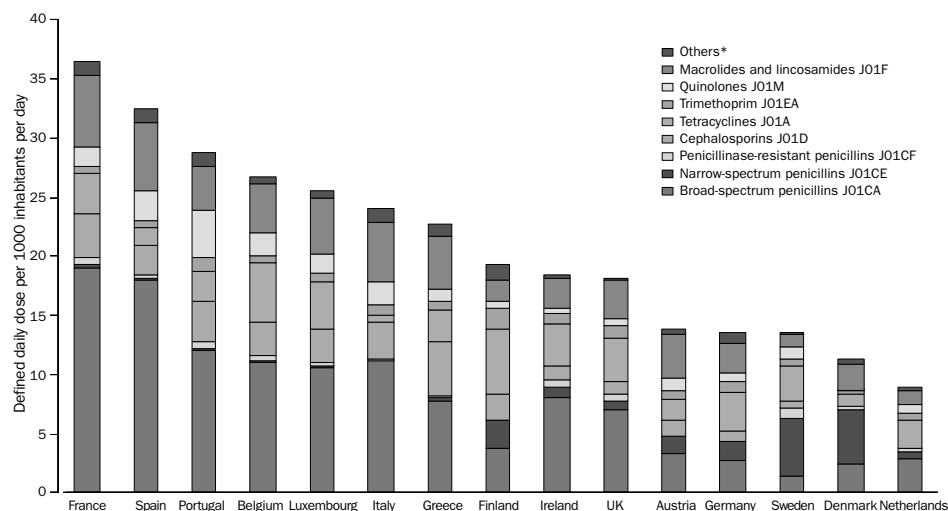


Figure 1 Outpatient antibiotic sales in 1997 in the EU. Reproduced from Cars et al. Lancet 2001

due to other factors such as a variation in access to specialists or relative price levels [13]. With the development of innovative technologies, new insights into disease processes and a greater interest in preventive medicines, it is not surprising that health care expenditures are increasing around the world in absolute terms and in the percentage of GDP. These trends unequivocally lead to choices that question whether the benefits of certain new and sometimes extremely costly medicines warrant making the products accessible on a wider scale—a balancing act between parsimony and profligacy that is usually decided on a national level [2,13].

Variation in medicines use may also be caused by (cross-national variation in) policies. The Herceptin® (trastuzumab) debate that raged in the United Kingdom (UK) media a few years ago illustrated the difficulties some patients encountered with the UK National Health Services (NHS). Many women were refused this medicine used to treat breast cancer because it had yet to be regulated by the National Institute for Health and Clinical Excellence (NICE) that advises the NHS on the cost-effectiveness of medicines [14]. That meant that breast cancer in-patients were getting Herceptin® in Wales, but in England they had to pay, thereby creating a variation in use across the UK. Another area of cross-national variation was found within relative effectiveness assessments (REAs). REAs are considered by national decision-makers when making reimbursement decisions to assess the net therapeutic benefit of interventions [15]. When comparing REAs among various countries, Kleijnen et al. (2012) concluded that some important methodological aspects for REAs, such as the decision to perform a comparison with ‘the best standard care’, are approached in a similar way in many countries [15]. However, other factors, such as study outcomes (clinically significant versus surrogate outcomes) varied across the EU countries included in this study. This study, as several other studies, did not include the level of medicines use in their study objectives. But it goes without saying that pharmaceutical policies affecting prices, reimbursement, marketing authorization, or clinical practice, may all affect the uptake and level of medicines use in the end.

### What do these studies tell us?

It is important to stress that there is not always consensus about what the optimum level of medicines use in various diseases is and that the “appropriate level” of use may vary because of the significance of the factors in multiple pharmaceutical systems and economies. In addition, there is no absolute wrong or right about which policies are effective, as policy implementation and effect might differ due to varying cultural and economic factors in countries. However, in some cases, good policies or good usage levels can be identified. Goossens et al. (2005), for example, showed that the variation of antibiotic consumption coincides with the occurrence of specific microbiological resistance at a country level, clearly indicating the positive effects of interventions designed to reduce antimicrobial medicines consumption at a national level in Europe [16,17].

The above-mentioned illustration shows that single causes of variation in medicines are often difficult to identify as various elements may play a particular role when analysing the use of similar medicines in multiple countries. In addition, it is likely that any given level of use of a specific medicine in one country is determined by a set of factors that might vary in another country as described in the examples above. In the last decade, an increasing interest has arisen

to study the variation in medicines use in an integrated way, including the combination of all relevant pharmaceutical system parameters. Several recent published international studies have shown variability in the utilisation of a wide range of medicine classes among European countries [13,18]. Thus, there is legitimate and understandable interest in how the use of medicines in one's own country compares to that in other countries. This interest does not only stem from policy makers, but also from the public. For instance, national patients' associations may lobby a government for new medicines use and make reference to the level of access in other countries. Furthermore, giving the public insight into cross-national variations in medicines use and the challenges that governments and health care providers face in providing safe, affordable and effective medicines will hopefully lead to a better understanding of the presence of restrictions in one's own country. Therefore, it is important to record the level of access of medicines in various countries and even more so to identify the reasons behind these variations. Studying medicines uptake across health care systems can provide information on how the outcome of the embedding process including access to and use of (new) therapies differs from one country to another. This may also be helpful in identifying best practices and improving public health, which may then improve the development of (national) policies and practice [6,8,19,20]. However, in some cases the impact of a national medicines policy is best studied at a national level. After all, some policies are clearly country-specific or have substantial unintended effects in specific patient groups and thus monitoring policy effects in individual countries is warranted as well.

## OBJECTIVES OF THIS THESIS

Although challenging, the importance of cross-national comparisons of medicines use or the cross-national comparisons of components of pharmaceutical care systems has been recognized [21]. Unfortunately, studies in this field often do not assess the relationship between medicines-usage data and data on important pharmaceutical care components. Studies have often solely presented aggregated data on major features of the national pharmaceutical or health system in various countries, such as number of physicians, life expectancy, and causes of death. The studies in this thesis take up this challenge and present aggregated data (data not on individual patients) on major features of the national pharmaceutical systems accompanied by actual usage data from multiple countries and across various medical conditions on either a global, European or national level. The findings in this thesis will be placed into three categories: global overview of national pharmaceutical policies and medicines use, understanding variation in medicines use in Europe and monitoring a specific policy in a single country. Finally, this thesis aims to guide future analytical work to better understand the extent and causes of variation in medicines use leading to better insights and policy in this important sector of modern life. The approaches and discussions as described in this thesis can be used as a start and will hopefully contribute to making evidence based and justified decisions on optimal medicines use in the future.

## OUTLINE OF THIS THESIS

This thesis includes nine studies divided into three chapters. After the introduction, **Chapter 2** presents a global overview of variation in existing national medicines policies and pharmaceutical consumption. *Chapter 2.1* is a historical review of the development of national medicines policies and includes an analysis of four political windows of opportunity, which served as the right moment to establish a national medicines policy. *Chapter 2.2*, written as chapter for the third edition of the World Medicines Situation Report (2011), examines global medicines consumption by volume within the non-hospital sector. Usage patterns across 84 countries, all income categories and a variety of healthcare systems are described.

In **Chapter 3** several multi-country studies are presented that explore possible factors of cross-national variation in medicines use in EU member states. This chapter starts off with *Chapter 3.1* that describes the main categories of critical issues in collecting national utilisation data on the use of TNFalpha inhibitors used to treat rheumatoid arthritis. *Chapter 3.2* explores the use of the same medicines as a measure of access to treatment with new (expensive) medicines. It assesses the relationship between several components of a pharmaceutical care system and the level of medicines use. *Chapter 3.3* and *3.4* focus on another class of medicines, newly approved medicines acting on the central nervous system. *Chapter 3.3* relates cultural diversity to cross-national variation in use. *Chapter 3.4* concentrates on the effects of variation in reimbursement decisions on the level and speed of uptake of the same group of medicines. Finally, *Chapter 3.5* focuses on the possible consequences of differences in the availability and uptake of new medicines for pharmaceutical care systems, in particular the contributions of EU member states to the EU regulatory network.

**Chapter 4** concentrates on a specific example of a reimbursement restriction on benzodiazepine use in the Netherlands. *Chapter 4.1* studies the impact of the reimbursement restriction in patients with a new diagnosis of a sleeping or anxiety disorder. *Chapter 4.2* assesses patient satisfaction with the information about this reimbursement restriction. In addition, patient opinions on the reimbursement restriction and their experiences after this policy measure had taken place are examined.

Finally, in **Chapter 5**, the general discussion, the studies in this thesis are placed in a broader perspective. Challenges of cross-national medicines utilisation studies on an aggregated level and the monitoring of policy effects are described. Finally, implications of this type of research for policymakers and society as well as directives for the future are presented.

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# CHAPTER 2

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INTERNATIONAL OVERVIEW OF NATIONAL MEDICINES  
POLICIES AND MEDICINES USE



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# CHAPTER 2.1

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## NATIONAL MEDICINES POLICIES – A REVIEW OF THE EVOLUTION AND DEVELOPMENT PROCESSES

Joëlle Hoebert, Liset van Dijk, Aukje Mantel-Teeuwisse,  
Hubert Leufkens, Richard Laing

*Conditionally approved for publication in South Med Rev*

## ABSTRACT

Medicines play a major role in protecting, maintaining and restoring people's health. Continuous provision of appropriate medicines of assured quality, in adequate quantities and at affordable prices is a concern for all national governments. A national medicines policy (NMP) developed in a collaborative fashion identifies strategies needed to meet these objectives, and provides a comprehensive framework to develop all components of a national pharmaceutical sector. This article is a historical review of the process of NMP development within health care systems as it occurred over the last 25 years worldwide. This increase is seen across all national income categories with the greatest rise in recent years in high-income countries. Nevertheless, not all countries have a NMP since political pressure by national experts or non-governmental organizations is often needed to establish a single comprehensive document. The analysis of four examples of a NMP formulation process shows that a political window of opportunity usually serves as a key element in reforming a NMP. Furthermore, the case studies demonstrate that the policy process is as important as the policy document, since the process creates a mechanism for stakeholders to come together and collective ownership of the final policy can be achieved. This may be crucial in view of the challenges to implement and monitor a NMP.

## BACKGROUND

Medicines play a major role in protecting, maintaining and restoring people's health. The regular provision of appropriate medicines of assured quality, in adequate quantities and at reasonable prices is therefore a concern for all national governments [1,2]. While overuse and misuse of medicines are common in many countries, the poor availability of essential medicines is a major problem in LMIC and for the poorer segments of the population [3]. In contrast to wealthier countries, up to 90% of the population in developing countries purchase medicines with out-of-pocket payments [4,5]. The emergence of new diseases, population ageing, increasing antimicrobial resistance, increasing use of preventive medicines and the availability of new expensive medicines displaying little or no therapeutic benefit over existing treatments, all contribute to increased spending on medicines across all income levels worldwide [6,7]. In addition to high expenditures, factors such as changing patterns of morbidity, the increasing role of the private sector in delivering medicines, health sector reforms and the presence or absence of health insurance schemes, and the effect of globalization and trade agreements also impact on access [8,9]. The existence of (or a combination of) these factors is country specific and relates to the national political situation, as well as the economical situation and existing legislation.

These access problems have persisted despite efforts by governments, development agencies and the World Health Organization (WHO) to improve access to essential medicines, to promote rational use and to ensure quality assured medicines are used. The reasons for the failure to achieve universal access and rational use are complex, may differ among countries, and involve a wide range of stakeholders. Thus, there is a general need for medicine policies based on universal principles, but nevertheless adapted to the national situation of a country, to meet the health needs of the inhabitants [10]. A national medicines policy (NMP) helps to identify strategies to meet these objectives, as it provides a comprehensive framework for the development of all components of the national pharmaceutical sector with a future perspective of 10 years to adapt to the changing environment, combined with monitoring and periodic reviews [10].

The final content of a NMP will vary among countries, as it is dependent upon cultural and historical factors, including a country's institutional capacity to regulate and enforce quality assurance, the political values of the government, the level of spending on pharmaceuticals, and economic development. As these factors develop continuously over time it is important to regularly update any NMP. Furthermore, the NMP must take into consideration that the elements are inter-linked and that a holistic approach is required; therefore, the development process must be clearly defined. The policy then becomes an expression of the government's commitment to provide medicines to the population and is a framework for action [11].

Since the first publication of WHO's 'Guidelines for Developing National Drug Policies' in 1988, many countries have tried to improve people's access to essential medicines by formulating a NMP [12]. This article reviews the historical development of NMPs, e.g. in terms of numbers and the development process across various income levels. In addition, the policy formulation process is examined in more detail with case studies from four countries.

## METHODOLOGY

This review is a quantitative and qualitative (describing the historical development) study of the development process and evolution of NMPs. The number of NMPs and their current status has been obtained from the results of the assessment of WHO Level I indicators conducted in 2007 [13]. Level I indicators measure the existence and performance of key national pharmaceutical structures and processes within countries. Finally, four examples of national medicines policy formulation processes are presented: Sri Lanka (small country with a long history of pharmaceutical policy innovation), Australia (high-income Western country with an integrated policy), South Africa (large country, political struggle needed for a radical change) and the former Yugoslav Republic of Macedonia (small country with a limited capacity and affected by civil disturbance in neighboring countries). These countries were chosen because they reflect diversity in the development process of the NMP and represent a range of economic status. Information about these processes was obtained using PubMed, the 2004 World Medicines Situation report and other literature sources. Three experts, closely involved in the policy formulation processes in three of the four countries, were asked by email to validate the descriptions of the policy processes.

## RESULTS

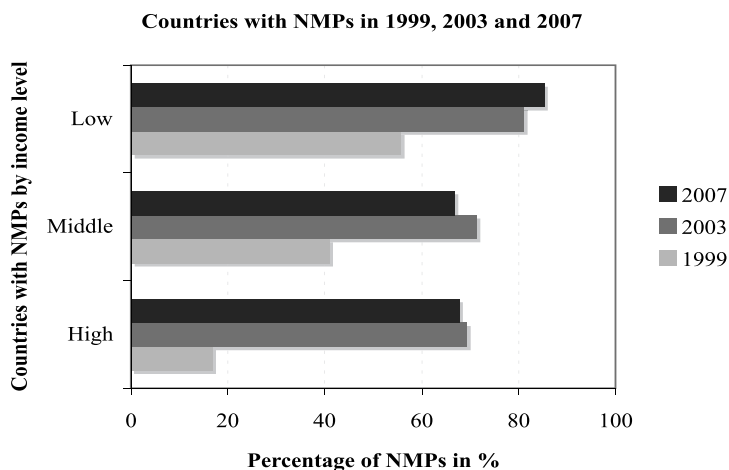
### Historical development of national medicines policies

#### *Role of World Health Organization*

In 1985, the Nairobi conference on 'The Rational Use of Drugs' took place [14]. The experts at the conference aimed to ensure access to essential medicines and rational use of medicines for all people, especially in developing countries. The outcome of this meeting was a recommendation that a NMP should be defined in each country to ensure that essential medicines of assured quality, safety and efficacy would be available at affordable prices to all people who need them at the right moment and at the right place and would be used appropriately. Primary responsibility for overseeing rational medicine use would rest with the individual member governments assisted by WHO. It was felt that at the international level WHO should disseminate guidelines on NMPs and this was eventually done in 1988 [1,12]. In 1989, 14 countries worldwide had formulated or updated a NMP within the previous 10 years [16]. Since then, many countries have formulated a NMP.

#### *Trends over time*

Increased awareness of the importance of a NMP in countries with limited resources is reflected by their early development in these countries. From 1985 onwards, the number of NMPs established in low-income countries increased rapidly, with the highest increase between 1985 and 1999. In wealthier countries, formulations of NMPs began only in 1995. Figure 1 shows trends for the formulation of NMPs from 1999-2007, by income level. It reveals that the percentage of NMPs increased across all income categories but the highest proportional increase was seen in high-income countries, from 18% to almost 70%.



**Figure 1** Trends in the formulation of national medicines policies (NMP), by countries' level of income, 1999, 2003 and 2007. Source: WHO level 1 survey 1999 (as appeared in the World Medicines Situation Report 2004), 2003 and 2007. Percentages are based on number of countries surveyed by WHO

### *Situation in 2007*

In 2007, WHO surveyed 156 countries and found that 132 (85%) countries had a NMP and 62 (40%) were supported by an official document updated within less than five years (see table 1).

Table 1 shows that low-income countries were more likely to have a NMP compared to high-income countries. Nevertheless, these developed countries have updated their NMP more recently than low-income countries. In addition, higher income countries seem to have more NMP implementation plans available than lower income countries. For many countries, the policy is drafted but may wait for years before full implementation.

### **Process of development**

A NMP involves a complex process of development, implementation and monitoring. First, the policy development process results in the formulation of a NMP. Secondly, strategies and activities aimed at achieving policy objectives are implemented by various stakeholders. Finally, the effect of these activities is monitored and the policy adjusted as necessary. Throughout the process careful planning, consideration of the political dynamics and the involvement of all stakeholders occurred. Besides the Ministry of Health, other key stakeholders can be found among regulators, professional organizations, producers, importers and distributors, health care professionals, patients and consumers, academics and civil society, health planners and managers, health finance authorities, insurance organizations, media and health/medicines donors, funders and major non-governmental organizations. Thus, it is important to identify political allies, and to maintain their support throughout the process [10,17].

The process of developing a NMP is almost exclusively a national matter and will differ among countries and regions with disparate income levels. In some countries, the NMP has been

**Table 1** Status of national medicines policies (NMP) by income level, 2007 [13]

	Country income level							
	Low (48)		Middle (73)		High (35)		Global (156)	
	responding countries	N yes %	responding countries	N yes %	responding countries	N yes %	responding countries	N yes %
NMP official (or draft) document	48	45 94%	73	61 84%	35	26 74%	156	132 85%
Official document updated < 5 years*	48	11 23%	73	32 44%	35	19 54%	156	62 40%
NMP implementation plan	45	32 71%	64	40 63%	28	22 79%	137	94 69%
NMP implementation plan updated < 5 years*	44	20 45%	64	31 48%	28	21 75%	136	72 53%
NMP integrated in National Health Policy	47	37 79%	60	44 73%	27	19 70%	134	100 75%

\*Since over 20% of countries with an NMP document / NMP implementation plan did not provide dates and very few indeed provided dates earlier than 5 years previously, it was assumed that those countries not providing dates had not updated their NMP document / NMP implementation plan in the last 5 years

introduced as a complete entity (though not necessarily implemented as such), but in other countries, the NMP is developed in components. In many low- and middle-income countries, a national essential medicines programme was the motivation for establishing such a policy and usually emphasized the selection, procurement, distribution and use of pharmaceuticals in the public sector [18]. During the last decade, these programs have recognised the importance of finance tracking, medicine prices and financial management [19].

In high-income countries, the strategic goals of a NMP are generally found in various laws, regulations, and administrative procedures—rarely in a single document. The lack of an integrated national policy is unsatisfactory from a public health point of view, as some policies affecting medicines seem to contradict or undermine others [17]. Although medicines policies have generally been developed at a national level in high-income countries, there has been increasing international harmonization among countries, which might be hampering the development of a NMP within a country.

In the past two decades, international trends in market-oriented health sector reforms for meeting new health needs and requirements have been underway or under consideration throughout the world and at all income levels. Although these trends may undermine public services and pose a threat to equity in the well established social-welfare systems of high income countries, such developments pose more immediate threats to the fragile systems in middle-income and low-income countries [20,21]. The pharmaceutical sector and its policies are influenced by health sector reforms with increased decentralisation, shifting roles and responsibilities from central department of pharmacy management to the district level and the establishment of district pharmaceutical management points. In a NMP, the policy must address the implications of an overall health system policy, although there are clearly aspects of pharmaceutical policy that must remain centralised—such as regulation, quality



assurance and public sector procurement. The process of deciding which functions fall into which area is complex and difficult and the decision to proceed, and the subsequent success of implementation, depends on political support and the capacity at a local level. Thus, the content of a NMP must be regularly monitored and adjusted as necessary.

Table 2 presents background information on population and economic data of the four case study countries. Full NMP development processes of these countries can be found in the appendix; the most important aspects of the development processes are outlined below.

*Sri Lanka's national medicines policy process: promoting generics despite opposition*

Two first attempt (1991 and 1996) to develop a NMP failed. Two important factors were the absence of participation by civil society and lack of health reform campaign by civil society organizations. Health Action International Asia – Pacific and its network partner 'The Peoples Movement for Rights of Patients' began lobbying for a NMP and convened a number of national seminars, meetings and workshops on the need for a NMP, which started a development process including all stakeholders in 2005. Although accepted by consensus and endorsed by the government in 2006, the current NMP has not been implemented due to strong lobbying by the private pharmaceutical industry against the NMP even though they had participated as a stakeholder. Generic promotion and substitution are two components in the NMP that the industry vehemently opposed and they have successfully lobbied to delay the implementation of the NMP.

*Australia's national medicines policy process: balancing health and economic objectives*

Australia, as a participant at the 39th World Health Assembly in 1986, contributed to the development of the strategy calling on governments to implement a NMP. In 1991, the Australian Government established the Australian Pharmaceutical Advisory Council (APAC) and the Pharmaceutical Health And Rational use of Medicines (PHARM) Committee. APAC's formation presented an opportunity for all interested parties to positively contribute on a multi-lateral

**Table 2** General statistics of Sri Lanka, Australia, South Africa and the former Yugoslav Republic of Macedonia

Countries	Sri Lanka	Australia	South-Africa	former Yugoslav Republic of Macedonia
Year of policy formulation	2006	1999	1996	2001
World Bank income level*	Lower Middle	High	Upper Middle	Upper Middle
Region	South East Asia	Western Pacific	Africa	Europe
Total population**	19.2	20.5	48.3	2.0
Gross national income per capita (PPP international \$)**	3,730	33,940	8,900	7,850
Life expectancy at birth m/f (years)**	69/76	79/84	50/53	71/76
Total expenditure on health per capita (international \$, 2006)**	213	3,122	869	623
Total expenditure on health as % of GDP (2006)**	4.2	8.7	8.6	8.2

\*Income groups are classified according to World Bank estimates of 2008 Gross National Income (GNI) per capita

\*\*Figures are for 2006. Source: World Health Statistics 2008

GDP = gross domestic product, PPP = Purchasing Power Parity

and consensus basis to the development of the NMP, while through the PHARM Committee and a multisectoral participatory process a policy for the improvement of medicines utilisation was formulated and adopted in 1992. In 2000 the first NMP was formally approved by the government with the overall goal ‘to meet medication and related health service needs, so that both optimal health outcomes and economic objectives are achieved’ [22,23]. To satisfy this goal, the policy framework addresses inherent tensions within the objectives of attaining affordable access to medicines, while maintaining a viable pharmaceutical industry, and achieving quality medicines and health systems.

#### *South Africa’s national medicines policy process: focusing on equity and access*

The focus of South Africa’s first single NMP was on equity. Under apartheid, the health care system was generous and highly effective, but only for the white population, and two separate draft national medicines policy documents were circulating. The key challenge for the new ANC-led government was to develop the ANC draft policy into a truly national policy, and WHO was invited to participate from the start. After one year the Minister of Health insisted that the process be completed and one policy document be prepared based on the three existing drafts (2 old drafts and a new document discussed with all stakeholders). This high-level political support resulted in the final policy document in 1996 [24]. This support also ensured that most of the national components of the policy were successfully implemented in the years that followed, although the new progressive medicine law was challenged in court by pharmaceutical industry and delayed for three years.

#### *Former Yugoslav Republic of Macedonia’s national medicines policy process: joint effort with WHO involvement*

Broad support from WHO in the FYR Macedonia, that was seriously destabilized by the Kosovo War in 1999 that led to an exodus of ethnic Albanians into Macedonia, created an opportunity to begin NMP formulation. Prior to the enactment of the Health Care Law in 1991 and the establishment of the Ministry of Health, the system of health care, although offering universal accessibility, was fragmented with little central governance or strategic overview [25,26]. In February 2000, the Ministry of Health and WHO Humanitarian Assistance Office in Skopje organized an initial meeting to discuss the implementation of a NMP and to present the main aspects of a NMP. In May 2001, several drafts were combined to produce one comprehensive document, which was officially endorsed by the FYR Macedonian government in October 2001.

## DISCUSSION

The number of NMPs around the world has increased over the past 25 years with an early increase in low-income countries and a more recent increase in high-income countries. Nevertheless, to date, not all countries have a NMP. If there is no political pressure by national experts or non-governmental organizations the need to establish a single comprehensive document may be absent. Low income and lower middle-income countries may be more likely to have a NMP, because access to medicines is a challenging problem for politicians. In addition, WHO

has focused on low- and middle-income countries since the 1980s. In high-income countries, access is generally assured, but complex issues related to rational use, medicines prices, reimbursement and industry concerns confront policy makers. Although most wealthier high-income countries have managed without a comprehensive NMP, they sometimes encounter problems due to a lack of a single NMP [17]. In most high-income countries components of a medicines policy are often in place, but are rarely addressed in a single comprehensive national medicines policy. In the USA, for example, matters tend to be managed separately by the Food and Drug Administration (FDA) (regulation), the Federal Trade Commission (FTC) (trading and competition issues), the National Institutes of Health (NIH) (research) and by individual states (dispensing). Moreover, states and professional associations develop and implement many different aspects of medicines policy.

The policy development processes of the four case studies show that the development of a NMP is a complex process that is country specific. Lessons learnt from the four described policy processes demonstrate that an appropriate political window is needed for the policy to be passed (for South Africa and the FYR Macedonia, a major political event acted as a trigger for initiating the policy development). Furthermore, all stakeholders must be involved at an early stage, and NMPs offer a stable system to guarantee access, and rational use of medicines. During the policy development process, countries are forced to consider a transparent framework so that stakeholders understand their roles and responsibilities and to define national priorities based on a balance between meeting patients' needs as well as ensuring effective use of the countries' resources and other incentives (e.g., maintaining a viable national industry as seen in the Australian case study).

Policy-making however, does not stop with the official adoption of a policy but should create mechanisms for implementation and monitoring. Large differences exist between NMPs in how the implementation is managed and funded. Unless there is a performance-related budget linked to the policy, good implementation (and monitoring) is unlikely to occur. The policy process of Sri Lanka clearly showed the struggle to implement the policy due to generics use guidelines, which the local industry opposed. A clear policy should be reassessed from time to time and revised as appropriate—ideally every 4-5 years. Sufficient staff with appropriate technical and professional capabilities are required [27]. Indicators or performance standards are a tool to determine whether adequate progress is being achieved and to assess the effects of changes on medicines policy objectives. Independent consultants or external professionals may be invited to complement a national evaluation team. Resources needed for these revisions should be allocated from the start of the development process. The NMPs of the four case studies show that although all policies address the importance of monitoring and evaluation, indicators for monitoring or an actual monitoring framework are often lacking within the policy. The NMP of the FYR Macedonia is the only policy that provides indicators for monitoring. None of the policies included independent external evaluation of the implementation of the NMP.

Although a NMP may indeed exist in a Ministerial Declaration or even in the law, and there may have been an implementation plan, this does not always mean that the policy works effectively. Shortcomings in regulatory performance, lack of access to essential medicines and

irrational use may exist despite the existence of a comprehensive policy document. An example of this shortcoming was seen in the failure to protect Australia (and other countries) from the COX-2 inhibitor regulatory failure [28]. Thus, a more complex NMP with major divisions of responsibilities between the central and state governments must include both the easily agreed-upon common interests but must also resolve the conflict areas in order to reach an agreed, national compromise involving all parties.

Although most pharmaceutical problems are best addressed at the national level through the use of NMPs, there could be cases where medicines policy issues are better managed at a regional or global level because some problems extend beyond the boundaries of national borders. There are many regional organizations working together to harmonise the regulatory aspects of NMPs and implementation of various aspects of the NMP, e.g. the European Medicines Agency (EMA) centralised registration process. Regional groupings such as ASEAN and COMESA are collaborating to harmonise regulation and pricing information and coordinate NMPs across countries within their regions. In conclusion, experiences in many countries have shown that pharmaceutical problems can best be addressed in a comprehensive policy, as piecemeal approaches can leave important problems unsolved. Case studies in four countries showed that the policy process is just as important as the policy document since the process must create a mechanism by which all stakeholders are brought together and a sense of collective ownership of the final policy may be achieved. This may be crucial in view of the challenges to implement and monitor the NMP.

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## APPENDIX: FULL DESCRIPTION OF NMP DEVELOPMENT POLICY PROCESSES

### **Sri Lanka's national medicines policy process: promoting generics despite opposition**

In 1959, Sri Lanka had a limited list of essential medicines and the use of generics was compulsory in public health care. The country's limited list of medicines was extended to the private sector in 1972, when the state became the sole importer of all pharmaceuticals through its trading arm, the State Pharmaceuticals Corporation, which also supplied the private market. The government's attempt to extend control to the private sector provoked controversy within the health services, private sector and industry, and particularly within the pharmaceutical industry. Cooperation with international organisations and non-governmental organisations was necessary to develop and implement a medicine policy that addressed the country's growing dependence on a number of multinational companies that monopolised the global trade in medicines [29]. In 1977, a new government came into power with neoliberal policies. The limited list of medicines was applied only to the public sector and the use of brand names and aggressive promotion of brands in the private sector returned. In 1991 an attempt was made to develop an NMP, but the attempt failed, as did a subsequent attempt in 1996. These efforts were not confined to the NMP alone; both in 1991 and 1996, a health task force was set up to recommend ways and means of restructuring the entire health service system. The documents they produced were accepted by the Ministry of Health, but were not endorsed by the government. Two important factors for this failure were the absence of participation by civil society in the two task forces and lack of health reform campaigns by civil society organizations.

In 2006 Sri Lanka succeeded in developing an NMP. In that year, the process was quite different from the previous attempts. Health Action International Asia – Pacific (HAIAP) and its network partner 'The Peoples Movement for Rights of Patients' (PMRP) began campaigning and lobbying for the formulation of an NMP and convened a number of national seminars, meetings and workshops on the need for an NMP. In 2005, two workshops facilitated by WHO/SEARO were held for all stakeholders, including representatives from the Ministry of Health, academia, health professionals and associations, trade unions, the private pharmaceutical industry and trade and civil society. HAIAP and PMRP took an active role and the NMP was accepted by consensus, forwarded to the Ministry of Health, approved by the cabinet, and passed by the Parliament in 2006.

The objectives of the current 2006 NMP for Sri Lanka for both public and private sectors are:

- 1) to ensure the availability and affordability of effective, safe and quality medicines relevant to health care needs of the people in a sustainable and equitable manner;
- 2) to promote the rational use of medicines by healthcare professionals and consumers;
- 3) to promote local manufacture of essential medicines [30, 31].

In the three years since the endorsement of the policy by the government, the Ministry of Health appointed a National Standing Committee (NSC) with 18 members representing all stakeholders and a mandate to implement the NMP. The NSC appointed a subcommittee to prepare a draft 'Act to Regulate Medicinal Drugs and Devices, Cosmetics, Neutraceutical and

Functional Foods’. The draft was presented to the Ministry of Health in early 2008; however, to date, little has happened. There was strong lobbying by the private pharmaceutical industry and trade against the NMP even though they had participated as a stakeholder. Generic promotion and substitution are two components in the NMP that the industry vehemently opposed and they have successfully lobbied to delay the implementation of the NMP. The PMRP has filed a fundamental rights petition in the supreme court of Sri Lanka asking the court to direct the Ministry of Health to implement the NMP. PMRP argues that any delay in the implementation causes a denial of the fundamental right of the people to access life saving medicines at affordable prices (Balasubramaniam K. Personal communication).

### **Australia’s national medicines policy process: balancing health and economic objectives**

Australia, as a participant at the 39th World Health Assembly in 1986, contributed to the development of the strategy calling on governments to implement an NMP. The need for an NMP was further illustrated in the ‘Health for All Australians’ document issued jointly by all State and Federal Australian Health Ministers in 1988. It was recognised that there was considerable medicine-related morbidity and mortality in Australia, much of which was preventable. There were, however, very few strategies or structures in place to support improvements in medication use. Furthermore, the research effort and knowledge of successful strategies to improve medication use was also limited, both within Australia and internationally. In 1989, the Consumers Health Forum widely circulated a document ‘Towards a National Drug Policy’ which crystallised the concept of an integrated medicine policy, and the need for action on how medicines are used. In 1991, the Australian Government established the Australian Pharmaceutical Advisory Council (APAC) and the Pharmaceutical Health And Rational use of Medicines (PHARM) Committee. Through the PHARM Committee and a multisectoral participatory process, a policy for the improvement of medicines utilisation was formulated and adopted in 1992.

Eight years later, in 2000, the first NMP was formally approved by the Australian government [22,23]. Under the auspices of the APAC, the policy integrated pre-existing elements within the new Quality Use of Medicines policy. The NMP was formulated in a partnership of government, healthcare professional organisations, the pharmaceutical industry, distributors, healthcare consumers and other stakeholders. APAC’s formation in 1991 presented an opportunity for all interested parties to positively contribute on a multi-lateral and consensus basis to the development of the NMP. Australia, with the most recent policy from a developed country, is one of the few developed countries with a comprehensive NMP. The Australian policy’s four major objectives are to ensure:

- 1) timely access to the medicines that Australians need, at a cost individuals and the community can afford, through the Therapeutic Goods Administration and through the Pharmaceutical and Repatriation Benefits Schemes;
- 2) that medicines meet appropriate standards of quality, safety and efficacy;
- 3) maintaining a responsible and viable national pharmaceutical industry; through the industry portfolio;
- 4) quality use of medicines [23].



The overall policy goal of Australia's NMP is 'to meet medication and related health service needs, so that both optimal health outcomes and economic objectives are achieved'. To satisfy this goal, the policy framework addresses inherent tensions within the objectives of attaining affordable access to medicines, while maintaining a viable pharmaceutical industry, and achieving quality medicines and health systems.

Political pressure by national experts and non-governmental organizations was a major influence on the development of Australia's NMP [11,32-34]. While much has been achieved in a decade, the development and marketing of new medicines, the use of new technologies and sources of medicines information, the costs of medicines, and perhaps most importantly, the increased interest consumers have taken in their health care, present further issues for policy development and implementation [35].

NMPs often do not address problems in other countries or what has been experienced when safety issues were at stake. Although this is a matter that concerns many countries, Vitry and colleagues showed that policy stakeholders failed to protect Australia from the COX-2 (cyclo-oxygenase-2) inhibitor regulatory failure, although Australia's NMP has aims that include quality use of medicines. They found that regulators did not appropriately warn prescribers about potential cardiovascular risks. The Pharmaceutical Benefits Scheme (PBS) did not limit unjustified expenditures on COX-2 inhibitors and pharmaceutical companies ran intense and misleading promotional campaigns on COX-2 inhibitors without adequate controls. Independent medicines information was insufficient to counter the effects of the millions of dollars spent on advertising in Australia. Their conclusion was that the core elements of the NMP, in particular the medicine approval process, the post-marketing surveillance system, the control of medicine promotion, and the quality of independent medicine information, required major reappraisal to avoid similar disasters in the future [28].

### **South Africa's national medicines policy process: focusing on equity and access**

In 1993, prior to the first democratic elections after apartheid, two separate draft national medicines policy documents were circulating. One was written by the government at the time, with input from academics at the University of Cape Town (a famous 'white' university) and another by the African National Congress (ANC). After a democratically elected ANC-led government was established in April 1994 under President Mandela, a national pharmaceutical policy committee was appointed by the Minister of Health with the following objectives:

- 1) develop a pricing plan for medicines to be used in South Africa in the public and private sectors;
- 2) develop a plan to ensure that medicines are tested and evaluated for effectiveness in the South African context of treatment using epidemiological approaches;
- 3) develop an Essential Medicines List to be used in the public sector and prepare treatment guidelines for health personnel;
- 4) develop specific strategies to increase the use of generic medicines in South Africa;
- 5) prepare a plan for effective procurement and distribution of medicines in South Africa, particularly in the rural areas;

- 6) investigate traditional medicines; and
- 7) rationalize the structure for pharmaceutical services [24].

The key challenge for the new government was to develop the ANC draft policy into a truly national policy, and WHO was invited to participate from the start. In November 1994, the committee presented a first report of its findings to the Minister of Health, and a new discussion document was disseminated based on the recommendations. This draft was used as the basis for wide consultations and discussions with health care providers, academia, other ministries, provincial and district representatives, professional organizations, pharmaceutical industry and patients. The process took time and after one year the Minister of Health insisted that the process be completed and one policy document be prepared based on the three existing drafts. This high-level political support resulted in the final policy document which was adapted by the Cabinet and published in 1996 [24].

The focus of the new policy was on equity. Under apartheid, the health care system was generous and highly effective, but only for the white population. Less than one quarter of the national health care budget was left for the remaining three quarters of the population along legally defined racial categories. The real challenge was to reduce overconsumption in the sophisticated parts of the system, e.g. the teaching hospitals, without losing their good quality and reputation, and make these facilities available for everyone, as well as using the savings to strengthen the rural services, which were the main source of care for the majority of the population. In all segments of the system, overuse and waste of medicines had to be reduced. Key tools, in this respect, were the development of national treatment guidelines and lists of essential medicines for all levels of health care. WHO contributed to the policy process by breaking the technical isolation that international sanctions had caused, and by supplying the government with information on practical experiences from successful countries, such as Zimbabwe and Australia. WHO also acted as an ‘honest broker’ to support the government to reach consensus among the various stakeholders, and helped develop and implement a five-year technical support programme—the South Africa Drug Action Programme (SADAP) [36].

The policy was largely successful, especially due to the political window of opportunity after the 1994 election and the high-level political support. Most of the national components of the policy (treatment guidelines, national medicine list, review of the national regulatory agency) were successfully implemented in the years that followed. However, the new medicine law, which included several progressive, but controversial, pricing policy components, such as generic substitution and parallel importation, was challenged in court by the research-based local and international pharmaceutical industry and delayed for three years. For various political reasons, some of the provinces remained skeptical and hesitated to become partners in the process. Yet, overall the policy was effective in making the government and the various stakeholders aware of the need for change, and in paving the way for the development of the pharmaceutical sector in the decade to follow. Several senior government officials, now in high office, were involved in SADAP in their formative years. The policy document of 1996 remains a strong text which can serve as an example for other countries [10, 37].

### **Former Yugoslav Republic of Macedonia's national medicines policy process: joint effort with WHO involvement**

The Former Yugoslav Republic (FYR) of Macedonia became independent in 1991 following the break-up of Yugoslavia and remained at peace during the Yugoslav wars of the early 1990s. However, the country was seriously destabilized by the Kosovo War in 1999. Following the exodus of ethnic Albanians from Kosovo into Macedonia and Albania at the end of the Balkan civil conflict, broad support from WHO in the FYR Macedonia also created an opportunity to begin NMP formulation. Prior to the enactment of the Health Care Law in 1991 and the establishment of the Ministry of Health, the system of health care, although offering universal accessibility, was fragmented with little central governance or strategic overview [25,26]. In February 2000, the Ministry of Health and WHO Humanitarian Assistance Office in Skopje organized an initial meeting to discuss the implementation of an NMP and to present the main aspects of an NMP. In April 2000, a group of 14 experts were appointed by the Minister of Health to work on the development and formulation of the NMP strategy document. Five working groups were created to develop specific elements of the policy: legislation and regulations, medicine selection, medicine information, rational medicine use, supply and economic strategies, and human resource development. Several meetings facilitated by international consultants were held before the NMP adoption workshop. In May 2001, several drafts were combined to produce one comprehensive document which was officially endorsed by the FYR Macedonian government in October 2001. While the Ministry and the Health Insurance Fund have continued to further develop and implement the medicines policy, a national working group completed an analysis of the pharmaceutical sector under the umbrella of the WHO Good Governance for Medicines Project [38]. In collaboration with the Ministry of Health, policy implementation will be supported in the future. The country's NMP includes a list of indicators for monitoring NMP implementation [39,40].



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# CHAPTER 2.2

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## GLOBAL PHARMACEUTICAL CONSUMPTION

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## ABSTRACT

This chapter examines medicine consumption by volume within the non-hospital sector. Usage patterns across 84 countries in all income categories and with a variety of different healthcare systems are described. The results show that consumption has grown in countries of all income categories. The percentage growth is higher in the low income countries than the high income countries, although in absolute terms the picture is reversed. Medicines to treat chronic disease are taking a larger proportion of total volume in the non-hospital sector. Projections indicate that chronic disease medicine volumes will need to increase dramatically if access is to be provided to those who need these medicines. Furthermore, usage of medicines included on the WHO Model List of essential medicines is similar across countries of all income categories, at about 25-35%. Higher country income is not associated with different use of the Model List products, and out of pocket expenditure is not necessarily associated with lower rates. The results also show that there is considerable variation in the share of Original and Licensed brand products both within and across product categories and countries as compared with Other Brands and Unbranded Products. This variation may represent an opportunity for policy intervention to encourage a shift in consumption to the generally cheaper unbranded categories of products. Finally, analysis of consumption is complicated by the diversity of databases and classification systems. Whilst the different systems can be viewed as being complementary, consumption patterns, and the impact of pharmaceutical policy in aggregate, could be clearer if data from the public and private sectors were combined. The need for more comprehensive information is particularly acute in low income countries.

## INTRODUCTION

Medicines are key to maintaining good health. In many developing countries medicines are effectively unaffordable or inaccessible. As shown elsewhere in the Report, total pharmaceutical expenditure in low income countries constituted around 30% on average of total health expenditure (range 7.7% to 62.9%). The expense of serious family illness, including medicines, is a major cause of household impoverishment.

This chapter focuses on consumption within the non-hospital sector and looks at whether and how the situation has changed over the last 10-15 years. Usage patterns across a large number of countries are examined and the proportions of medicines to treat chronic and acute diseases compared. The extent to which medicines included on the WHO Model List of Essential Medicines are used and the use of generics is discussed. These analyses highlight issues for policy makers in low and middle income countries that affect both infrastructure and policy.

## METHODOLOGY

### Data Sources and methods of medicine classification

Analysis of information on volumes of medicines consumed is difficult as such information is often collected in different ways for different purposes by different organizations using different definitions (see box 1). Procurement organizations may collect or report information from purchases or tenders. Health insurance or reimbursement organizations are likely to report expenditures and volumes of specific or categories of products, but only for those products approved for reimbursement. Market research organizations are likely to report purchases by pack but rarely for low income countries, and in such countries, public sector information is often not included. Whilst analysis of information on expenditures is interesting, and is reported in another chapter of this Report, expenditure information cannot provide a complete picture of consumption as prices vary greatly for the same product across countries, over time and under different circumstances - as is shown in the pricing chapter of the Report.

Governments have used commercially available databases such as those from IMS Health to investigate medicine consumption across countries, and both EuroMedStat and ESAC have used and compared the data available produced by national health systems with those collected by IMS for particular therapeutic categories. In high income countries the information on volumes from administrative databases and that collected by IMS is similar. For middle and low income countries, however, IMS data consist of either a combination of both public and private sector sales, or private sector sales alone. In these countries, conclusions drawn only from administrative data may be very different from those using IMS data.

IMS data and classifications were used in this chapter for two reasons – first ease of use and comparability as discussed above, and secondly the need to look at long term trends. Long term trend information has often not been collected from the public sector in many middle and low income countries - if only because public sector reimbursement of medicines, particularly those used in the non-hospital sector, has often been a relatively new phenomenon. The IMS data are thus often the only source of data on consumption in earlier periods.

### Box 1. Standardisation of pharmaceutical volumes

There are two systems that have attempted to standardize data collection on pharmaceutical consumption by volume. The first is the WHO-ATC/DDD system coordinated by the WHO Collaborating Centre in Oslo. This centre has defined a five level system of classifying medicines by Anatomical, Therapeutic and Chemical criteria. Each molecule can be described by a unique alphanumeric code. A Defined Daily Dose (DDD) has been defined as the assumed average maintenance dose per day for a pharmaceutical used for its main indication in adults.

The European Pharmaceutical Market Research Association (EphMRA) developed and maintains the EphMRA ATC which classifies medicines into four levels. The first level is the broadest group, for example, “C”, drugs working on the “Cardiovascular System”. The fourth level is the narrowest group, for example C2A1, “Antihypertensives plain, mainly centrally acting”.

Work has continued since 1991 to align the WHO and EphMRA ATC systems for all mono substances in a given class as listed in the WHO ATC Index, mainly at the 3rd level and above. In this Chapter, analyses are carried out at either the first level or third level.

These two systems (WHO ATC/DDD and EphMRA ATC/IMS SU) should be seen as complementary. Each has been developed for a particular purpose but both allow comparisons of volume or medicines consumed to be made.

IMS developed and maintains the Standard Unit (SU) as a measure of volume. The IMS Standard Unit is a measure of volume based broadly on an assumption about the smallest identifiable dose given to a patient, dependent on the pharmaceutical form. The SU thus attempts to describe the likely dose taken by a patient at any one time whilst the DDD is an estimate of the total amount of a drug that an “average” patient would take in a day for the drug’s main indication. A DDD may therefore be equivalent to an SU, or a multiple of an SU, depending on the strength of, for example, a tablet.

Data from IMS can be converted to WHO ATC/DDD data formats but this has to be done at a molecule level, taking regard of the pharmaceutical form and the strengths, quantities or volumes within each pack. This might be done when data are to be compared with data from other sources, for example from public sector systems. This is possible for a single therapeutic group but cannot reasonably be done for all medicines across many therapeutic classes and countries.

This chapter focuses on consumption within the non-hospital sector. This is not because the hospital sector is unimportant but because volume information in the hospital sector is, at least within high income countries, often unavailable, even within commercial databases. The non-hospital sector information can generally be split from the hospital sector within the IMS databases, and usually constitutes the larger volume. Given the lack of available hospital data for many countries, therefore, analysis was restricted to the non-hospital sector although in order to extend country coverage a minority of the countries’ data used (6 out of 84) related to both hospital and non-hospital sectors, or hospital sector alone (Denmark, Malaysia, Singapore, Slovenia, Sweden and China). Robust data on volumes or particular categorizations were not available for all 84 countries in every year. The lowest number of countries included in any analysis was 73. Information on which countries’ data were unavailable is given in each section.



In interpreting the volume trends described below the following comments should be borne in mind:

- IMS collects relatively few data relating to consumption of medicines in Central and East Africa, despite good coverage of French speaking Africa and parts of North Africa. The patterns of medicine consumption described here for low income countries as a group could thus be very different if more comprehensive data were available.
- The decision to focus on the non-hospital sector does not mean that the same set of medicines or conditions were always being compared, particularly over different time periods. The range of medicines distributed in the non-hospital sector differs by country and has differed over time. In some countries, for example, like Bulgaria or China, medicines used within hospitals are sometimes purchased from the non-hospital sector.
- The IMS non-hospital sector data for high income countries is almost entirely paid for by some form of taxation or insurance. In middle income countries, the IMS data tend to reflect a mix of funding sources and in low income countries the data generally reflect out of pocket expenditure alone. This does not prevent comparisons being made but it will affect the types of questions that can be asked and the conclusions that can be drawn
- Changes to the distribution system can also affect the range of medicines monitored by IMS, as will changes to IMS' coverage of that system.
- IMS data represent either purchase or dispensing by the supply chain, rather than actual consumption by patients

## Definitions

This chapter uses a number of different concepts to classify medicines and countries. These are described below.

### *Medicines*

Protection: Medicines are classified according to whether or not a product has benefited from protection from competition in the form of, for example, product patents or data exclusivity. Products that are categorised as "Protected" are products that are currently protected from competition. Products that are categorised as "No longer protected" are products that once benefited from protection, but for which this protection has now ceased or expired. Products that are categorised as "Never protected" are products that have never benefited from protection. This classification depends on the availability of robust information on patents. This information is only available in the IMS data for 25 countries and these are described in the relevant section below.

Licensing: Medicines are also classified separately according to the relationship between the originator of the molecule and the company that is marketing the product. Products that are marketed by the originator of the molecule are defined as "Original Brands". Products that are marketed under the terms of a licensing agreement with the originator are defined as "Licensed Brands". "Other Brands" constitute two different types of product. The majority of "Other Brands" are branded products that are either manufactured and/or marketed

by a company that is not the originator of the molecule, and for which there is no evidence of a licensing agreement, for example, branded generics, pirate products and copy products. A number of “Other Brands” are also branded products that contain ingredients for which there are no originators, i.e. the ingredients are derived from naturally occurring substances. Examples are vitamins, homeopathic medicines and infant milks. Some insulins are also classified as “Other Brands”. “Unbranded products” are products that are manufactured and/or marketed under the generic name of its ingredient molecule(s), rather than a brand name. This classification applies even if the product is launched before the estimated patent expiry date of the active molecule ingredient, and/or marketed by the molecule ingredient originator and a licensee of the originator. These definitions are applied as the product is launched and do not change with, for example, patent expiry. An “Original or Licensed Brand” may therefore be “Protected” or “No longer Protected”. The licensing categorisation is available in all but 10 (Algeria, Croatia, Estonia, India, Kuwait, Latvia, Lebanon, Lithuania, Romania and Ukraine).

Chronic/Acute: Third level EphMRA ATC classes are categorised according to whether that class was thought to be more likely to treat chronic disease or acute disease. The classification was based principally on an analysis of 14.6 million prescriptions issued to 1.1 million patients in the 12 months to September 2008 taken from a sample of General Practices in the UK. Classes were first defined as acute or chronic on the basis of the average number of prescriptions written per patient in that year. If the average for a class exceeded 2 prescriptions, the class was assigned to “chronic”. For example most antibiotics and analgesics were classified as acute whereas asthma and diabetes medicines fall into the chronic disease category. Some classes with less than an average of 2 prescriptions per patient per year were also assigned to “chronic” following review. The classes that were reassigned tended to be specialist products that are less likely to be recorded as being used within a General Practice database but which are nevertheless used to treat chronic disease.

Essential medicines: The definition of essential medicines was derived from the WHO Model List. For the latest data period (2008), the most recent WHO Model List available at the time was used (2007). For earlier time periods, the list most appropriate to that time period was used. The WHO Model List contains a core and complementary list and both lists contain medicines that may be substituted by any other medicine within the same pharmacological class. Those medicines that may be substituted are marked by a square box symbol. The WHO Model List specifies the molecule name, the form and the strength of the medicine. In this Chapter, medicine volumes are attributed to WHO Model List usage on the basis of molecule name and form alone. Strength was not used to filter out volume. This analysis will thus tend to over-estimate WHO Model List usage as all strengths, rather than just those shown in the WHO Model List, are included. Substitutable medicines were defined in this chapter as those medicines falling in the same EphMRA ATC3 class.

### *Countries*

Income: World Bank income categories for 2008 were used to classify countries. These ratings were also applied to data from earlier years. This means that comparisons over time represent

comparisons between the same set of countries. In some cases data from IMS were only available as groups of countries. The data from Central America for example is an aggregate of 6 countries (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama), and the data from French speaking Africa is an aggregate of 10 countries (Benin, Burkina Faso, Cameroon, Congo, Gabon, Guinea, Ivory Coast, Mali, Senegal, Togo). These countries fall into different income categories. For the purposes of this chapter the aggregate data were classified according to which income category was predominant. Thus French speaking Africa was categorized as low income (7 out of the 10 countries are low income countries), and Central America as lower middle income (4 out of the 6 countries fall into the lower middle income category).

## RESULTS

### Pharmaceutical consumption in the non-hospital sector

#### *Per capita consumption*

Table 1 shows the change in median pharmaceutical consumption per capita according to countries' level of income between the years 2000 and 2008. 2000 is the earliest year for which the majority of countries' data are available, 2008 was the latest calendar year for which data were available at the time of analysis. Growth in consumption within the non-hospital sector occurred across all income categories. High income countries as a whole consumed very much more than lower income countries, although some higher income countries did post volume declines over this period, notably France. It should be remembered also that these data reflect patterns in the non-hospital sector only and that volumes for the public sector in the low income countries are not included.

Growth in volume was highest in the low income countries. In middle income countries growth followed the gradual expansion of public sector financing of medicines into the non-hospital sector. In low income countries, however, where out of pocket expenditure is the main source of finance for the consumption shown here, other factors must be at work. One factor affecting all countries is the growing burden of chronic disease. The impact of chronic diseases on consumption patterns is examined specifically in later sections.

**Table 1** Per capita pharmaceutical consumption in the non-hospital sector by country income category (by volume, 2008 in SU)

	Median per capita consumption, 2008	Multiple of median SU per capita to that of low income countries	% change in median annual per capita consumption (2000 versus 2008)
High (n=31)	1042	7.7	18.6%
Upper middle (n=15)	515	3.8	20.4%
Lower middle (n=19)	214	1.6	22.9%
Low (n=12)	135	1.0	29.3%

Of the 84 countries, the following were excluded from this analysis: Israel, Netherlands, Puerto Rico (H), Croatia, Russia (UMI) and Algeria, Ukraine (LMI)

For the rate of growth in volumes between these two dates

### *Analysis of consumption by EphMRA ATC class*

Just five classes of medicines account for more than two-thirds of total volume and of these, four are common to all income groups in both 2000 and 2008 (see Table 2). Systemic general anti-infectives (Class J) are used more widely in low income countries. In low income countries this class had a higher share (7.3%) compared to cardiovascular medicines (Class C) (4.3%). The importance of infectious diseases in low income countries is reinforced by an examination of medicines used in the treatment class P (Parasitology). These medicines are almost absent in 2008 within high (0.2%) and upper middle (0.4%) income countries but take a relatively high volume share in low income countries (3.5%).

### *Consumption of acute and chronic disease medicines*

In this analysis, groups of medicines at EphMRA ATC Class 3 level were classified as being used to treat mainly either acute or chronic disease (for methods and definitions, see methodology. From Figure 1 it can be seen that those medicines classes used mainly to treat chronic disease constitute an increasing proportion of total volume across all income categories, although acute disease maintains a significant share. The median percentage of products used to treat chronic disease is consistently less for lower income countries than for higher income countries, reflecting the greater burden of infectious diseases in lower income countries.

The growth in chronic disease medicine volumes is not unexpected. Chronic disease is forecast to increase dramatically in the developing world. The projected impact of chronic disease has been estimated for the 23 developing countries with more than 80% of the chronic disease burden in 2005. Deaths due to chronic disease were projected to rise by 48% between 2005 and 2030, and disease burden (Disability-Adjusted Life Years (DALY) lost) by 20%. A DALY is a summary measure that combines years of life lost due to premature death and years of life lived with disability.

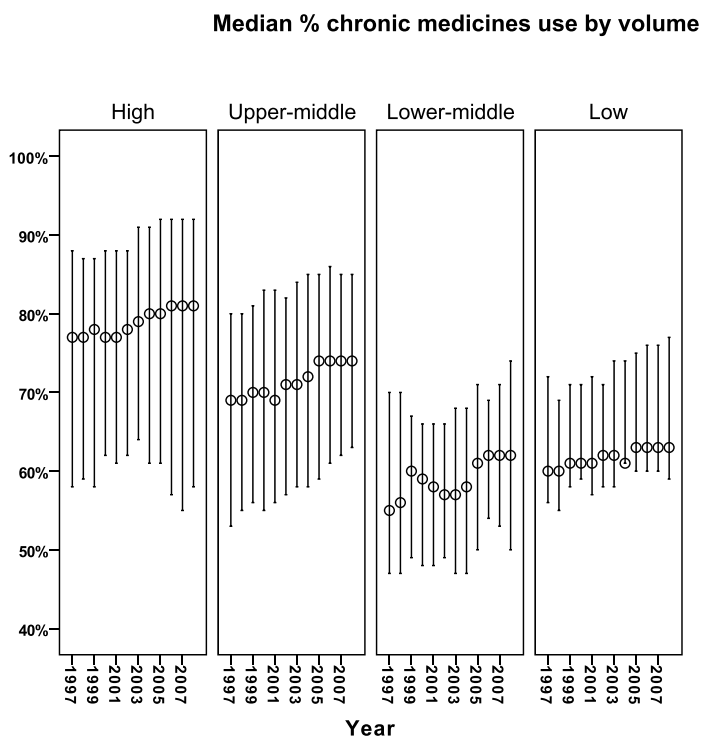
The impact of such growth on absolute volumes, as opposed to expenditure, is relatively unexplored. An analysis was therefore carried out to estimate the absolute volume increase needed to treat patients with Type 2 diabetes in two middle income countries, and indeed what effect wider usage would have on morbidity and mortality. Diabetes is a significant cause of

**Table 2** Consumption of major classes of medicine by country income category in the non-hospital sector, 2008

EphMRA ATC class	% total consumption by major classes of medicine, 2008 (growth compared to 2000)			
	High (n=31)	Upper middle (n=15)	Lower middle (n=19)	Low (n=12)
A alimentary tract and metabolism	16.6 (-1.7)	17.4 (-1.7)	22.7 (-0.9)	23.9 (0.3)
C cardiovascular system	15.6 (3.0)	11.9 (1.3)	7.7 (1.4)	4.3 (0.8)
N central nervous system	16.6 (2.5)	12.9 (-1.4)	9.1 (-0.6)	13.7 (-0.4)
R respiratory system	12.8 (-2.5)	19.8 (0.3)	14.5 (-0.7)	17.3 (1.9)
S sensory organs	12.8 (0.4)	12.2 (0.3)	13.2 (-1.1)	12.7 (-2.4)

Growth compared to 2000 is shown between brackets. Of the 84 countries, the following were excluded from this analysis: Israel, Netherlands, Puerto Rico (H), Croatia, Russia (UMI) and Algeria, Ukraine (LMI)

For percentage growth in volumes between these two dates



**Figure 1** Comparison of medicine classes used to treat chronic diseases in the non-hospital sector as a proportion of total volume among different WHO country income categories between 1997 and 2008 (median and range)

chronic disease burden and by 2025 approximately three-quarters of those with diabetes will live in developing countries. The methodology and results are described in box 2.

### *The use of essential medicines by country income category*

The WHO Model List of essential medicines is a guide for the development of national and institutional essential medicine lists. Medicines were categorized according to whether or not they were included within the WHO Model List (For more information on essential medicines and the WHO Model List see Chapter on Selection in this Report, and for the methods and definitions used here, see methodology).

Figure 2 shows the percentage of total volume that is made up by medicines listed on the core and complementary WHO Model List of Essential Medicines (2007), as well as those medicines that are permitted to be substituted for those on the core and complementary lists. It is important to note that the IMS data from low income countries excludes publicly reimbursed medicines, and that in middle income countries the information from the public hospital sector is not included. A key comparison is between the public sector in high income countries and the private sector in low income countries. This is because these represent on the

### Box 2. Type 2 diabetes and its impact on morbidity and mortality

The study used information on treatment volumes collected by IMS from the public sector in South Africa and the public and private sector in Brazil. Information on prevalence and current access to treatment were derived from the literature. Analysis was restricted to the public sector in South Africa due to the absence of information on prevalence of diabetes in patients treated in the private sector. Analysis covered both public and private sectors in Brazil.

Target levels of usage of antidiabetic medicines were derived from the cohort of patients placed on an intensive glycemic control programme as described in the ADVANCE trial, a factorial randomized, controlled trial conducted at 215 collaborating centres in 20 countries from Asia, Australasia, Europe, and North America.<sup>1</sup> At the time of the analysis, intensive treatment had been found to provide a 10% relative reduction in the combined outcome of major macrovascular and microvascular events as compared to standard control regimens, although more recently published trials may appear now to give a different picture.

The estimated change to current volumes if intensive treatment were introduced is shown in Table 3.3 below. Estimates are given for two levels of patient access – 15% and 60%. If a 60% target is chosen, the estimated required increases (in WHO DDDs) for oral antidiabetics in Brazil is more than 200% and well over 300% in the public sector in South Africa. Negative values indicate that current volumes exceed those needed to reach target levels in that level of patient access.

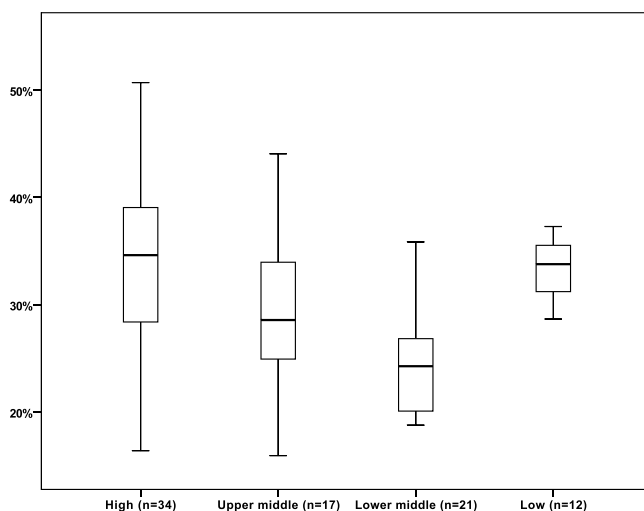
**Table 3** Estimated change to current volumes if intensive treatment introduced in two middle income countries

		Increase in volume needed to intensively treat	
		Only 15% of all diabetes patients	Only 60% of all diabetes patients
South Africa (public sector)	Metformin	16.50%	366%
	Sulfonylureas	48.80%	495%
	Insulin	-62%	52%
Brazil	Metformin	-13%	248%
	Sulfonylureas	-12%	254%
	Insulin	44%	475%

1 The ADVANCE Collaborative Group. *Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes*. New England Journal of Medicine, 2008; 358: 2560-2572.

one hand national or insurance funded expenditure in public sector facilities and on the other out of pocket expenditure in private facilities. Middle income countries in IMS data represent a mix of funding. Having said this, there appears to be little difference between country income categories, and the situation has changed little since 2002. Median usage of medicines on the Model List ranges on average between 25% and 35% across all income categories.

There are a number of reasons why the use of medicines included in the WHO Model List may be so low, but these are likely to be different in the various income categories. In low

**% Model List (core, complementary and substitutable) of total volume, 2008**

**Figure 2** Percentage of total volume, and interquartile range, in the non-hospital sector in 2008 made up by medicines listed on the core and complementary WHO Model List and medicines that are permitted to be substituted for those on the core and complementary list issued in 2007

income and some middle income countries the level will be a function of the fact that here the private sector serves to both supplement and complement the public sector. The mix of medicines stocked in the private sector will thus tend to be different to those procured by the public sector. Given the mix of funding sources in middle income countries, however, it might have been expected that the rate of WHO Model List usage would have been higher than that seen in low income countries. However it is clear from the data from high income countries that a higher income, and wider public reimbursement of medicines, does not necessarily correlate with greater or lesser use of the WHO Model List products.

### Consumption of brands and/or generics

#### *Percentage of volume in the retail sector by type of brand in 2008*

As discussed earlier, IMS data can be divided into two broad categories: Original brands plus Licensed brands and Other brands plus Unbranded medicines (For definitions see methodology).

In 2008, the share (in volume) of Other Brands and Unbranded was more than twice that of Original and Licensed brands across all income categories (see Table 4). The share of Original and Licensed brands was highest in the high income countries but similar in both middle and low income countries. There has been modest decline (2-3%) in the percentage of Original and Licensed brand usage since 2000. The higher % use of Original and Licensed brands in high income countries no doubt reflects their higher use of on-patent products. These similarities however hide considerable variation between countries in the use of generic medicines as shown in the next section.

**Table 4** Percentage share of Original and Licensed Branded Medicines, of different types of medicines in the non-hospital sector by country income category in 2000 and 2008

<b>2000</b>	<b>High (n=31)</b>	<b>Upper Middle (n=12)</b>	<b>Lower Middle (n=18)</b>	<b>Low (n=12)</b>
Median	38%	23%	22%	30%
Minimum	7%	6%	7%	10%
Maximum	57%	38%	32%	31%
Percentile				
25	33%	18%	14%	20%
75	46%	30%	30%	30%
<b>2008</b>	<b>High (n=31)</b>	<b>Upper Middle (n=12)</b>	<b>Lower Middle (n=18)</b>	<b>Low (n=12)</b>
Median	35%	20%	19%	28%
Minimum	17%	9%	6%	6%
Maximum	55%	38%	33%	31%
Percentile				
25	26%	16%	10%	17%
75	44%	23%	25%	29%

The following countries were excluded from this analysis in both 2000 and 2008: Estonia, Kuwait, Netherlands (H), Croatia, Latvia, Lebanon, Lithuania, Romania (HMI), Algeria, India, and Ukraine (LMI)

### *Consumption of generics in higher income countries*

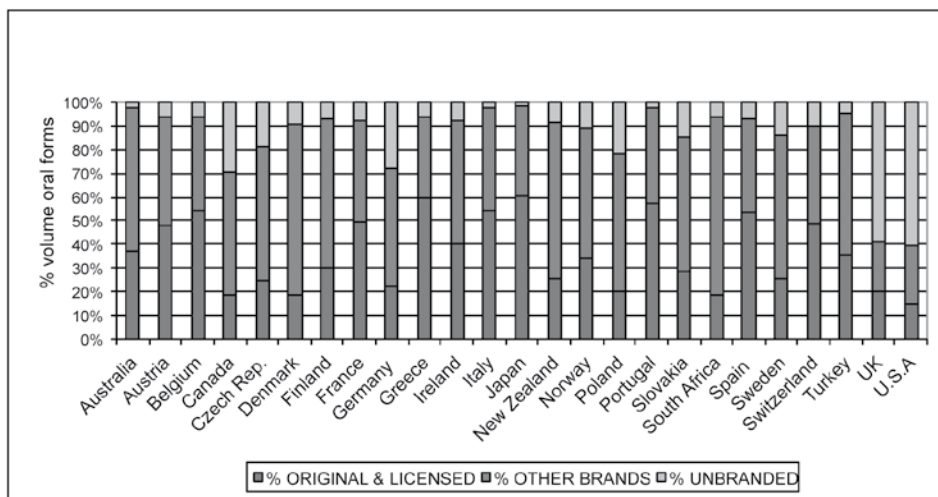
In 25, mainly high income, countries, the IMS consumption data can be broken down according to the existence of legal or commercial protection from competition (see methodology for definitions). This allows analysis of only that part of total consumption that has never been protected against competition or for which protection has expired or ceased (the “Unprotected” market). Figures 3 and 4 show a breakdown of the Unprotected market for oral forms in the non-hospital sector for all 25 high and upper middle income countries for 2000 and 2008.

As noted above there is considerable variation between countries in the usage of the different types of product. It is clear that the US, UK, Canada and Germany use a substantial amount of unbranded (generic) medicines while several other countries still rely heavily on Original or Licensed branded products even though their protection has expired or ceased years previously. In the higher income countries described here, it may be that reference pricing, rebates paid by the wholesalers or pharmacists, regional or national procurement contracts or other reimbursement policies lead to little or no differential in the price of the original or licensed brand and the equivalent unbranded generic at some or all of the points within the distribution chain. It is only where this is not the case that wider use of unbranded generics would produce savings and policy needs to take these factors into account.

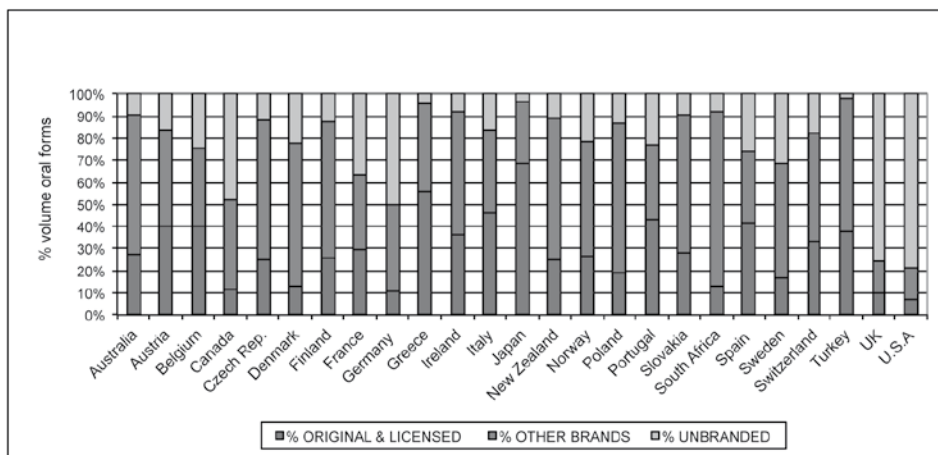
### *Consumption of generics in lower income countries in the non-hospital sector*

In lower income countries the difference in price between Original and Licensed brands and their branded or unbranded generic equivalents can be great. For example in a review of the WHO/HAI pricing studies published recently the “percentage difference in price between originator brands and lowest-priced generics (brand premium) in the private sector was over





**Figure 3** Volumes of oral forms in the unprotected market, 2000



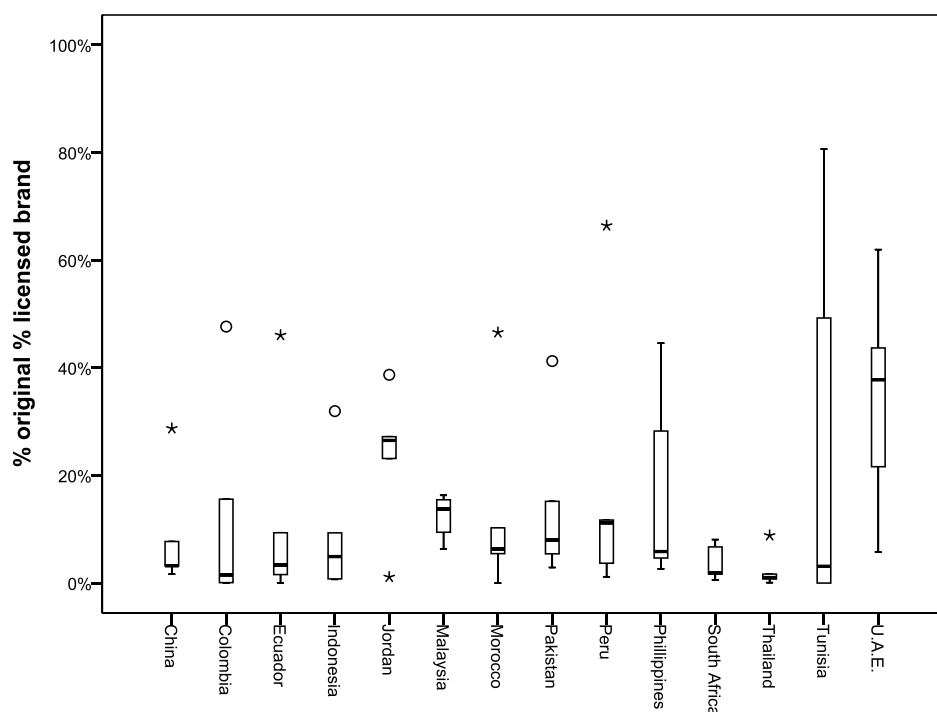
**Figure 4** Volumes of oral forms in the unprotected market, 2008

300% in lower-middle income countries and low income countries, whereas in upper-middle income countries it was substantially lower (152%), and in India it was only 6%." [1].

As explained in the methodology section, in lower income countries it is not possible within the IMS data to split out the Unprotected Market. However it is possible to look in some detail at some widely used molecules. Figure 5 shows how the share of volume of original and licensed brands varies for each of five commonly used medicines from different therapeutic classes. Each of these medicines had generic equivalents according to the WHO/HAI survey.

Outlier products whose market share was more than 1.5 times the Inter Quartile Range (IQR) for the country are indicated by open dots. Outlier products whose market share was more than 3 times the IQR for the country are indicated by asterisks.

Even within this small sample of products it can be seen both that the usage of Original and Licensed brands varies both by medicine and across countries. Again such variation may offer an opportunity for savings if there were greater use of generics. However branded generics have sometimes been found to be priced at the same price of the original or licensed brands and the perception of the relative quality of branded or unbranded generics and indeed their relative pricing in each country has had a significant effect on consumption patterns.



**Figure 5** Consumption of original and licensed branded versions of 5 commonly used medicines (aciclovir 200mg, atenolol 50mg, ciprofloxacin 500mg, omeprazole 20mg and simvastatin 20mg) in the non-hospital sector in the year to September 2009 (as a percentage of total consumption)

## DISCUSSION

The current and projected growth in volumes seen here will challenge the healthcare budgets of both individuals and governments, and perhaps also the supply chain itself. As demand grows, unless systems and resources improve, the rate of stock outs, already too high in both public and private sectors in the developing world, may worsen.

The analyses in this chapter suggest some useful areas for further investigation at an individual country level that will help to address these two issues:

- Whilst the intra and inter-country variation in the use of generic medicines is not necessarily indicative of inconsistent policy, it does suggest that a review of the different incentives and requirements for generic prescription, dispensing and substitution, and their implementation, may generate substantial savings.
- The role of the private sector supply chain should be considered. The impact of dramatically increased volumes on the reliability of supply may be better managed using the skills and resources of both sectors than either alone. Lessons from the Medicines Transparency Alliance may be relevant.
- The 25-35% share of medicines listed on the WHO Model List of essential medicines being consumed may indicate that a local review of consumption patterns of products on the national list is appropriate, if this has not been done already.

These actions, and assessment of their impact, will benefit from comprehensive information covering both public and private sectors. In lower income countries, particularly those in sub-Saharan Africa, what information that is available is spread across a number of different databases and sources. Efforts to link such sources of information on price, volumes and expenditure together should be encouraged.

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# CHAPTER 3

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UNDERSTANDING VARIATION IN MEDICINES USE  
IN EUROPE





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# CHAPTER 3.1

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## **QUALITY AND COMPLETENESS OF UTILISATION DATA ON BIOLOGICAL AGENTS ACROSS EUROPEAN COUNTRIES: TUMOUR NECROSIS FACTOR ALPHA INHIBITORS AS A CASE STUDY**

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*Pharmacoepidemiology and Drug Safety. 2011 Mar;20(3):265-71*

# ABSTRACT

## Introduction

For optimal decision making on access to and regulations around biologicals, availability of national utilisation data is a prerequisite. This study characterises the main categories of critical issues in collecting available national utilisation data on tumour necrosis factor alpha (TNFalpha) inhibitors in different European countries.

## Methods

Data were collected on characteristics of the nature of TNFalpha inhibitors usage data and on usage of TNFalpha inhibitors itself (2003–2007). Utilisation rates were expressed as defined daily doses (DDDs)/1000 inhabitants/day. Data from Denmark, Finland, Ireland, the Netherlands, Norway and Portugal were included.

## Results

Characteristics of TNFalpha inhibitors (usage settings and ways of distribution to patients) and databases (type of data collected, public availability and data sources) influenced the way data were collected and determined the type of research and policy questions that can validly be addressed. The prevailing differences in the structure of national databases are prohibitive for critical aspects of medicines utilisation studies. An increase in TNFalpha inhibitors usage over time was observed in all countries and varied widely from 0.32 (Portugal) to 1.89 (Norway) DDDs/1000 inhabitants/day (2007).

## Conclusions

In the European countries studied data on national TNFalpha inhibitors usage is not easily, if at all accessible. Intercountry collaboration and sharing of technical resources will facilitate harmonization of data collection allowing independent, population based, health and outcomes research.

## INTRODUCTION

Modern biotechnology agents, such as tumour necrosis factor alpha (TNFalpha) inhibitors, significantly altered the treatment paradigm of rheumatoid arthritis (RA) therapy from treating to preventing symptoms [1,2]. Biologicals are now being prescribed earlier and more often as combination therapy than they were 5 years ago [2,3]. Also new indications (i.e. psoriasis plaques, M. Crohn) for these agents have been approved opening additional therapeutic windows [4].

A number of independent academia-initiated but industry sponsored medicines registers have been set up by several national rheumatology societies in European countries to monitor their long-term safety and effectiveness and to make sure that benefits from clinical trials are confirmed in clinical practice [5–7].

With the exception of RA registers in e.g. Denmark and Sweden, most biologics registers are not-population based and catchment areas are not always known [5,7–9]. Besides, biologics registers exist in only a limited number of countries for a limited number of diseases and medicines. Even if the catchment area is known, the data can not be easily extrapolated to cover the whole population. An Australian study has shown that access to anti-rheumatic biologicals varied considerably among different regions [10]. The utilisation roughly correlated with the per capita ratio of rheumatologists. Other factors like patient's income, indirect costs and cultural beliefs also influenced the use of specialist care. Geographic variation in access to biologicals has also been identified in the United Kingdom (post-code prescribing) [11] whereas a recent study conducted in the US showed geographic variation in Medicare pharmaceutical spending in general [12]. Prospects of people diagnosed with RA seem to be substantially influenced by geographical location [13].

For governments, regulators or policy analysts, who have to decide on what medicines should remain/be subsidised, who should have access, what restrictions should apply to access and what a reasonable distribution would be between reimbursement and the individual contribution, data covering the whole population are essential and should be easily available. Affordability of and access to these types of medicines are becoming increasingly problematic for healthcare systems and individuals, as healthcare resources are finite and innovative biological medicines are very expensive [14]. Consequently it is vital that in individual countries, a system designed to collect data about the actual and total consumption of these medicines is in place, either by a medical records or an administrative database [15,16].

So far no other studies have assessed the methodological difficulties in collecting and analysing (publicly) available national utilisation data for biologicals. Studies have looked at problems in collecting comparable data for small molecules in Europe using different types of databases to obtain the full picture of medicines consumption [17–19]. Although these studies provided valuable information, additional issues may be encountered when collecting usage data for biologicals, because of the nature of these medicines (e.g. various distribution ways, intravenous or subcutaneous administration).

Therefore, the aim of this study was to identify and assess in terms of policy implications, the methodological problems one encounters when collecting national usage data on biologicals in a sample of different European countries using TNFalpha inhibitors as an example.

## METHODOLOGY

### TNFalpha inhibitors

In Europe until 2008, three TNFalpha inhibitors, infliximab (Remicade®), etanercept (Enbrel®) and adalimumab (Humira®), had been approved by the Committee for Medicinal Products for Human Use (CHMP) [1,20–22]. Although not all TNFalpha inhibitors were initially approved for RA, by 2007 all three TNFalpha inhibitors have had several approved indication extensions including RA, see Table 1. All of these TNFalpha inhibitors were included in the present study.

### Data collection

Data collection was realised with support of the European PILLS (Post-Innovation Learning Cycle for Pharmaceuticals) network, an international research network involved in the study of the effects of pharmaceutical policies in medicines use [23]. Eleven countries were approached to participate in this study. Finally, six European countries were included in this study providing a balanced sample in terms of heterogeneity of healthcare and pharmacy systems, reimbursement rules and availability of usage data. These countries included Denmark, Finland, Ireland, the Netherlands, Norway and Portugal.

Two different types of data were collected for this study, i.e. questionnaire data on specific characteristics related to the availability of TNFalpha inhibitors usage data as such and quantitative utilisation data.

#### Questionnaire data

Information was collected on the following determinants that could influence the way data was collected on TNFalpha inhibitors utilisation: public availability of the databases, type of data collected, usage setting of the TNFalpha inhibitors and means of distribution to patients.

#### Utilisation data

Table 2 shows an overview of the sources used for the extraction of the utilisation data. The anatomical therapeutic chemical (ATC)/defined daily dose (DDD) methodology was chosen as method for presenting drug utilisation data [24]. The DDD is a dosage measure determined by

**Table 1** Initial approval indications and approved indication extensions for infliximab, etanercept and adalimumab

Indication approved by EMA	Date of issue of marketing authorization by EMA		
	Infliximab	Etanercept	Adalimumab
Crohn's disease	13-08-1999	-	04-06-2007
Rheumatoid arthritis	27-06-2000	10-05-2004	08-09-2003
Ankylosing spondylitis	15-05-2003	16-01-2004	01-06-2006
Psoriatic arthritis	24-09-2004	05-12-2002	01-08-2005
Plaque psoriasis	29-09-2005	24-09-2004	19-12-2007
Ulcerative colitis	28-02-2006	-	-
Juvenile idiopathic arthritis	-	03-02-2000	25-08-2008

EMA = European Medicines Agency

**Table 2** Data sources (as used in 2009)

Country	Data source	Data type	Hospital data included?	% of inpatient use for 2007	Coverage population	Years covered
Denmark	DKMA	Sales	Yes	±100%	100%	2003 - 2007
Finland	NAM	Wholesaler	Yes	44%	100%	2003 - 2007
Ireland	HSE	Claim	No		100%	2003 - 2007
	IMS Health	Sales	Yes	8%	100%	2003 - 2007
The Netherlands	GIP	Claim	No	Not available	100%	2003 - 2007
	Farminform	Sales	Yes		>98%	2006 – 2008
Norway	Norwegian Institute of Public Health	Wholesaler	Yes	Not available	100%	2003 - 2007
Portugal	CEFAR	Dispensing	No <sup>a</sup>		100%	NA <sup>a</sup>
	IMS Health	Sales	Yes	100%	100%	2003 - 2007

a = until 2007, use of TNFalpha inhibitors is restricted to hospitals, DKMA = Danish Medicines Agency, NAM = National Agency for Medicines, HSE = Health Service Executive, IMS = Intercontinental Marketing Services, GIP = Drug Information Project, CEFAR = Centre for Health Studies and Evaluation, NA = not applicable

the World Health Organization and is based on the assumed average daily maintenance dose for its main indication use in adults [18,24]. Utilisation data were obtained for products with ATC codes L04AB01 (etanercept), L04AB02 (infliximab) and L04AB04 (adalimumab) and covered the period 2003–2007. For infliximab, the DDD is 3.75mg, for etanercept 7mg and for adalimumab 2.9 mg [25]. DDDs used in this study are the DDDs for the main indication (RA) and resemble the usual dose for RA as reflected in the current national guidelines (e.g. the DDD of etanercept is 7 mg and the usual dose for RA is 50 mg weekly) [26–30]. The data, available on a yearly basis, were obtained from ambulatory, hospital or total care. The data were presented on an aggregate level in DDDs/year or in DDDs/1000 inhabitants/day [25]. In order to achieve collection of consistent and comparable data, the country representative of each participating country was required to provide the data by means of a specially developed and standardised questionnaire.

### Data analysis

Utilisation rates (DDDs/1000 inhabitants/day) 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. For the Netherlands, inpatient data were only available for the years 2006–2008 whereas outpatient data were available for the period 2003–2008. Since the ratio between the in- and outpatient use for 2006–2008 was relative constant (1.65, range 1.59–1.69), this ratio was also used to calculate the missing inpatient use for the years 2003–2005.

## RESULTS

Various factors influenced the ease of data collection. Some factors were specifically related to the way TNFalpha inhibitors are used in clinical setting, other factors were related to the way data are available and collected.

## Factors related to TNFalpha inhibitor usage

Due to the intravenous/subcutaneous administration routes and for monitoring of adverse events, treatment with TNFalpha inhibitors is initiated by a specialist, mainly operating in hospitals. If patients are well-instructed and able to self-administer these medicines, treatment may be continued at the patient's home. Portugal is the only country in which the use of TNFalpha inhibitors is limited to hospitals only (until 2007). In the other countries, outpatient dispensing is an exclusive task of community pharmacies, except for the Netherlands where outpatient distribution of etanercept and adalimumab is realised via two channels; pharmacies and specialised distributions centres. These distributions centres receive the orders through the Internet and deliver the products by mail or courier service [31,32].

The various ways in which TNFalpha inhibitors are distributed affect the capturing of national utilisation data. Dispensing, and/or wholesales data should be able to cover usage from either inpatient or outpatient but sales data from wholesalers to community pharmacies in general will not cover hospital data. Claims data will be most likely to include data from both settings. Due to the specific distribution systems in the Netherlands, data from a third delivery route should be covered by the database as well. Depending on the source (claims, wholesales or dispensing data) these data will or will not be included.

## Factors related to the databases

### *(Public) availability of the databases*

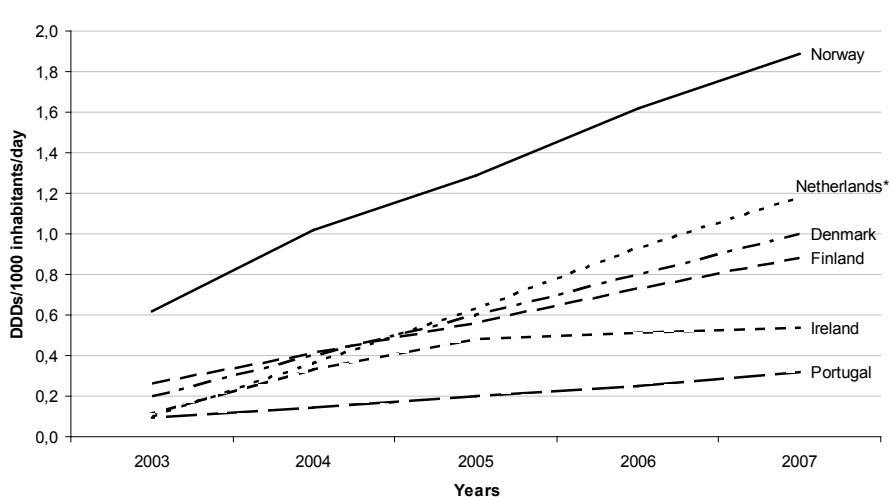
Finland, Denmark and Norway provided national utilisation data available in the public domain. To capture utilisation data from Ireland and Portugal collaboration with country representatives was necessary. Both representatives had unrestricted access to outpatient TNFalpha inhibitor utilisation data. Hospital sales data for these countries were provided through their contracts with IMS Health. TNFalpha inhibitor utilisation for the Netherlands was captured using a public (outpatient) and a non-publicly (in- and outpatient data) available database. The latter did not cover the full study period. Both sources captured usage distributed by the unique deliveries.

### *Data collection – type and setting*

Only Finland, Denmark and Norway included data from both the in- and outpatient setting within one source. In the Netherlands one database did capture both data from the in- and outpatient setting but another database was required to obtain total national utilisation over the full study period. The data used in this study all come from administrative databases, who generally record information as a by-product of financial transactions. In Ireland and the Netherlands, the databases involved captured different types of data, outpatient data were captured by claims data whereas inpatient data were captured by sales data. To capture medicines utilisation in the four remaining countries, sales data were used in both Portugal and Denmark, whereas wholesale data were used in Finland and Norway. All data sources covered more than 98% of the total population. No database was able to give information on patient characteristics (age, gender and/or diagnosis) or off- label use. All data could be converted into one common unit of measurement (DDDs/1000 inhabitants/day).

## Utilisation data

Large variations over time were observed in overall utilisation (Figure 1). For the year 2007, utilisation of all TNFalpha inhibitors varied strongly and ranged from 0.32 DDDs/1000 inhabitants/day for Portugal to 1.89 DDDs/1000 inhabitants/day for Norway. An increase in use over time could be demonstrated for all countries.



**Figure 1** Trend over time of TNFalpha inhibitors usage defined in Defined Daily Dose /1000 inhabitants/day. \*: Inpatient data 2003 – 2005 based on ratio between in- and outpatient data in 2006-2008. Therefore, 2003 – 2005 represent estimated (inpatient) and actual data (outpatient)

## Consequences for pharmacoepidemiological and policy research

The specific characteristics of TNFalpha inhibitors influence the kind of databases available for data collection and consequently (co)determine the type of research questions that can validly be addressed. Table 3 reflects the situation in which databases, capable of collecting national utilisation data on biologicals may or may not be suitable. This table shows that data collection is more complicated with respect to data on biologicals. Pharmacoepidemiological studies are feasible as based on these data but only at an aggregated level. The databases are generally less detailed in their clinical contents but yet are often representative and complete while covering large patient populations including elderly patients, children and those in nursing homes, all of them being most often underrepresented in or totally excluded from clinical trials. Within the field of pharmaceutical policy research these data are valuable and can help provide answers to new public health questions as they can be linked to relevant system characteristics such as guidelines and reimbursement restrictions or country characteristics such as pharmaceutical expenditures and gross domestic product.

**Table 3** Possibilities and limitations of biological usage data on medicines utilisation studies

Possibilities	Effect of biologicals
To link system (such as reimbursement regulations) and cultural characteristics to medicines utilisation	More complicated as several databases are required
To link medicines utilisation to country related factors, like GDP and pharmaceutical expenditures	More complicated as several databases are required
To study time trends in medicines consumption on a national level	More complicated. Not all countries are able to collect this kind of data on a national level or for the same time period
To study time trends in medicines consumption between countries	More complicated as less countries are able to provide data
Limitations	
Adjust for potential important confounders such as smoking status, alcohol use and body mass index.	More complicated due to data type
To study medicines consumption for specific indications	More complicated due to data type
To perform a cross sectional analysis (observation at a defined time)	More complicated because of multiple types of data and multiple data sources (error around time point will influence observation).

## DISCUSSION

The main purpose of the present study was to set out critical methodological issues related to the collection of TNFalpha inhibitor usage data in various European countries. Critical issues that were encountered were the (public) availability, the type of data collected and the specific distribution routes and clinical setting in which TNFalpha inhibitors are used. Although some of these are generally known for all kind of data collections for pharmaceutical policy and regulatory purposes, this study shows that acquiring insight in the usage of biologicals seems to be a particular challenge. When no single comprehensive database exists, national usage data can only be collected by using multiple sources like dispensing, wholesale and claims data. The specific characteristics related to the TNFalpha inhibitors such as direct delivery of TNFalpha inhibitors to patients, and both in- and outpatient utilisation complicate data collection further as different databases are (sometimes) required to obtain the complete picture of actual consumption. In the present study, more than one database was required to capture national TNFalpha inhibitors utilisation, in four out of the six countries. In this relation, the Netherlands probably provide a key example of complexity of the various delivery routes of TNFalpha inhibitors. Distribution can be organised through hospitals, pharmacies and/or specialised distribution centres. Portugal provides an example of a country that has an effective system in place that collects usage data for the outpatient setting. Nevertheless, data collection becomes complicated when it concerns medicines used in the inpatient setting. In all situations more standardisation of data collection would be helpful to improve comprehensive national collection of utilisation data, to enable cross-country comparison and to avoid an over-/underestimation or double counting of the actual consumption. Some databases cover the



whole population; others use a sample to collect utilisation data, and then extrapolate these data to cover the entire population. This is normally seen as valid for estimates of prevalence or incidence. Double counting or extrapolation corrections are constant factors within a database and will not influence the trend over time of TNFalpha utilisation as shown.

The (public) availability of the data is also a critical element. Availability may differ from restricted access (data as property of a specific institution/organisation) to unrestricted access (data available in the public domain), with or without payment. This study showed that public availability increases the ease of data collection not necessarily leading to inferior quality of the data; the public available databases of the Nordic countries included data on the number of people treated with immunomodulating agents although it was unknown for which indication, which specific agent and whether they were counted double when using multiple immunomodulating agents. For databases, like IMS, data on the hospital sector is not always available. This is in part because data for some countries is based on only a sample, which might lead to over- or underestimation or because the distribution system is complicated which troubles data collection (e.g. the Netherlands). For policy makers involved in making decisions such as for evaluating the clinical and economic effects of medicines reimbursement policy changes, in countries where a national register is lacking or without contracts with commercial databases, public available databases are important.

Another factor that may hamper the interpretation of our data is the fact that we sampled European countries on the basis of the willingness of selected key national officials to participate, availability of usage data and heterogeneity of healthcare system processing prescriptions and dispenses of TNFalpha inhibitors. Reasons for not participating were (i) non-response to the questionnaire sent ( $n = 3$ ), (ii) national medicines utilisation monitoring systems were not (yet) operational as the finance method of the TNFalpha inhibitors changed during the last 10 years. Inpatient data could sometimes not be provided as the costs (when values are transformed to volumes) of TNFalpha inhibitors used in hospitals were subsumed into the overall hospital budget rather than being specifically identifiable or within a specific budget ( $n = 1$ ) and (iii) non-availability of data was considered a political sensitive issue, therefore data could not be given to third parties ( $n=1$ ). Although these factors may have induced some selection bias, we believe that the primary aim of the study, i.e. to identify and assess in terms of policy implications the methodological problems one encounters when collecting national usage data on TNFalpha inhibitors has not been jeopardised. The array of identified methodological challenges for utilisation research on such a clinically relevant drug class is in our view comprehensive and valid.

The methods we used to quantify the utilisation data may have some limitations as well. The DDD methodology was chosen as it enables comparison of use within the category as well as it enables time comparison of the changing patterns across different countries when data on a patient level is not available. However, the DDD methodology should be handled with caution when recommended dosages differ from one indication to another and where the prescribed daily dose (PDD) may differ from one population to another (e.g. according to sex, age, ethnicity or geographic location). For infliximab, the concept of DDDs has important limitations as the dose is weight-based, differs between indications and dose-escalations are

frequent, as are changes of the infusion interval. For this study, however, we assumed that these differences would occur in all studied countries and would therefore not influence the trend as seen. But when the assessment of reliable utilisation rates is the main goal of a study, this should be taken into account.

The volume of TNFalpha inhibitors consumed varied substantially between the different European countries studied. The highest usage was reported for Norway and the lowest amount of usage reported for Portugal. An increase in use over time was reported for all countries. Further studies should be conducted to reflect on the differences in usage seen between countries and take different indications into account.

In conclusion, this study shows that current data capture methods for TNFalpha inhibitors usage are heavily influenced by the practice of healthcare and pharmacy systems delivering these products to patient care. This study emphasises the need for more coordination between (local) registers in order to enhance the collection of comparable national utilisation data. Ideally patient registers would cover the whole population. However using the current data with their acknowledged limitations gives a rather quantitative indication of usage not available by any other means. It also provides insights into the trend in consumption of these agents. Improved intercountry collaboration and related sharing of technical resources will facilitate the harmonisation of data collection efforts and the development of a standard methodology will help to improve international data on medicines consumption allowing not only useful healthcare planning but also independent, population based, health and outcomes research [33–35].

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# CHAPTER 3.2

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## DO RHEUMATOID ARTHRITIS PATIENTS HAVE EQUAL ACCESS TO TREATMENT WITH NEW MEDICINES? TUMOUR NECROSIS FACTOR ALPHA INHIBITORS USE IN FOUR EUROPEAN COUNTRIES

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## ABSTRACT

### Introduction

To explore the use of the biological tumour necrosis factor alpha (TNFalpha) inhibitors used in the treatment of rheumatoid arthritis as a measure of access to treatment with new medicines. In addition, characteristics both related to national health systems and spending will be assessed to explore possible differences in international utilisation.

### Methods

Data from four European countries were included: Ireland, the Netherlands, Norway and Portugal. Annual utilisation rates of TNFalpha inhibitors (2003–2007) were expressed as defined daily doses (DDDs)/1000 inhabitants/day. Qualitative data such as country characteristics, national health policy characteristics, guidelines were obtained from the literature. In addition, interviews were held with leading rheumatologists of each country to put obtained results into (cultural) context.

### Results

Utilisation of TNFalpha inhibitors varied widely from 0.32 (Portugal) to 1.89 (Norway) DDDs/1000 inhabitants/day (2007). A major driver for the utilisation of TNFalpha inhibitors seemed to be the country's total health expenditure ( $R_2 = 0.81$ ). When the use of TNFalpha inhibitors became more established, the association seemed stronger. Differences in health expenditure were nevertheless not the only determinant of usage. Cultural aspects such as difference in recognition of guidelines also come into play when looking at differences in TNFalpha inhibitor utilisation between countries.

### Conclusions

The prospects of patients receiving TNFalpha inhibitor treatment depend on the country where they are living. In case uniformity of management and treatment would be considered to provide health benefits, the extent and the causes of variation should feature prominently on future public health agendas.



## INTRODUCTION

The introduction of biologicals for the treatment of rheumatoid arthritis (RA) marked a major step forward in the management of this disease and created a paradigm shift in the treatment of RA. Biologicals are now being prescribed earlier and more often as combination therapy than five years ago [1–4]. Remission of disease is now the primary therapeutic aim, which can be achieved through intensive treatment strategies [5]. However, biologicals for treating RA are expensive; annual treatment costs for biologicals in the first year range from about D 13.500 to D 15.000 [6,7]. Treatment costs have become an important concern associated with the use of these biologicals. Western European health care systems aim to achieve optimal health and economic outcomes for society as a whole as well as for the individual patient. Governments strive to ensure affordable access to a wide range of prescription medicines equitably across all areas and to all patients [8]. However, individual governments may take different measures to achieve this goal, which may result in variable access to these biologicals.

Variation in access to medicines is seen in practice, even within a single country. An Australian study reported that within a country, those in equal need may not have equal opportunities to access rheumatologic services [9]. Geographical variation in access to biologicals ('postal code prescribing') has also been identified in the United Kingdom [9,10]. A recent report on international variation in medicines usage commissioned by the UK Department of Health, examined how medicines usage varied between countries. For the disease RA, the UK usage of biologicals ranked relatively low compared to 13 other European Union (EU) countries [11]. The reasons for these variations were diverse and sometimes difficult to establish. Differences in health spending and systems did not appear to be strong determinants of usage, but clinical culture and attitudes towards treatment did. For example, the use of biologicals in Australia roughly correlated with the per capita ratio of rheumatologists, and this varied considerably between geographical regions [9]. On the other hand, another study trying to explain the variations in uptake of biologicals did note differences in national income (as measured by gross domestic product (GDP)) as a possible explanation [12]. The relative impact of each explanatory factor is likely to differ among systems [7,13,14].

While the authorisation of biologicals is centralised by the European Medicines Agency (EMA) and the clinical evidence base available to the national societies issuing clinical guidelines is largely the same, the management of diseases as well as pharmaceutical policies and therefore the usage of biologicals may vary widely across Europe. Building on previous reports on access to treatment in RA, the objective of this study was to further explore the use of the biological tumour necrosis factor alpha (TNFalpha) inhibitors used in the treatment of RA as a measure of access to treatment with new medicines by studying national health systems and spending characteristics. In addition, we aimed to add opinions from key leading rheumatologist to put the obtained results into (cultural) perspective.

## METHODOLOGY

To enable comparisons of medicines utilisation between countries, datasets with a comparable structure need to be available. Factors that should also be taken into consideration, such as regulatory and budgetary constraints, reimbursement policies and cultural factors should all be well documented. In addition, we aimed to select countries that were similar in size, but also representing a certain geographical and variation in gross domestic product and health expenditures that exists within Europe. Based on these criteria, four countries were selected, namely Portugal, Ireland, Norway and the Netherlands.

### Regulatory situation

In Europe until 2008, three TNFalpha inhibitors, infliximab (Remicade®), etanercept (Enbrel®) and adalimumab (Humira®), had been approved by the Committee for Medicinal Products for Human Use (CHMP) [15–18]. Although not all TNFalpha inhibitors were initially approved for RA, by 2007 all three TNFalpha inhibitors have had several approved indication extensions including RA, see Table 1. All of these TNFalpha inhibitors were included in the present study.

### Population and disease characteristics, national health policy characteristics and budgetary constraints

Population and disease characteristics (e.g. population size, prevalence of RA), specific national health policy characteristics, such as reimbursement restrictions and national guidelines, and data on budgetary constraints, such as GDP, total health expenditures (THE) and total pharmaceutical expenditures (TPE) related to these countries were retrieved from various public sources [7,19–23]. Price information was retrieved from GÖG PPI System 2011 and included ex-factory prices (per unit) of all available package sizes, as of October 2004 and June 2007.

Four key leading rheumatologists of each participating country were interviewed in 2009 to comment on the differences seen in utilisation according to the cultural context and clinical attitude towards TNFalpha inhibitors. The interviewed rheumatologists were Professor J.A.P. da Silva (Portugal), Professor B.A.C. Dijkmans (the Netherlands), Professor T.K. Kvien (Norway) and Professor D.J. Veale (Ireland). They all play an active role in their national societies of

**Table 1** Initial approval indications and approved indication extensions for infliximab, etanercept and adalimumab

Indication approved by EMA	Date of issue of marketing authorization by EMA		
	Infliximab	Etanercept	Adalimumab
Crohn's disease	13-08-1999	-	04-06-2007
Rheumatoid arthritis	27-06-2000	10-05-2004	08-09-2003
Ankylosing spondylitis	15-05-2003	16-01-2004	01-06-2006
Psoriatic arthritis	24-09-2004	05-12-2002	01-08-2005
Plaque psoriasis	29-09-2005	24-09-2004	19-12-2007
Ulcerative colitis	28-02-2006	-	-
Juvenile idiopathic arthritis	-	03-02-2000	25-08-2008

EMA = European Medicines Agency

**Table 2** Data sources (as used in 2009)

Country	Data source	Data type	Hospital data included?	Coverage population	Years covered
Ireland	HSE	Claim	No	100%	2003 - 2007
	IMS Health	Sales	Yes	100%	2003 - 2007
the Netherlands	GIP	Claim	No	100%	2003 - 2007
	Farminform	Sales	Yes	>98%	2006 - 2008
Norway	Norwegian Institute of Public Health	Wholesaler	Yes	100%	2003 - 2007
Portugal	CEFAR	Dispensing	No <sup>a</sup>	100%	NA <sup>a</sup>
	IMS Health	Sales	Yes	100%	2003 - 2007

a = until 2007, use of TNFalpha inhibitors is restricted to hospitals,, HSE = Health Service Executive, IMS = Intercontinental Marketing Services, GIP = Drug Information Project, CEFAR = Centre for Health Studies and Evaluation, NA = not applicable

rheumatology and in the European League Against Rheumatism (EULAR). Interviews followed a semi-structured guide to allow adaption to the background of the rheumatologists and country-specific circumstances and inclusion of additional relevant information. The interviews covered the following three main themes: hurdles to perform an adequate treatment of RA, opinions on current treatment options and future directions of RA treatment. The information gathered in these interviews has been included in the result and discussion section, and served as country specific examples.

### Utilisation data

Collection of TNFalpha inhibitors utilisation data was realized with support of the European PILLS (Post-Innovation Learning Cycle for Pharmaceuticals) network [8], an international research network (network members working in academic institutions or at national health agencies) involved in the study of the effects of pharmaceutical policies in medicines use. Table 2 shows an overview of the sources used for the extraction of the utilisation data. For Norway and Portugal, sales data from the Norwegian Institute of Public Health and IMS Health, respectively, were retrieved. A combination of sales and claim data were used to cover the utilisation for the Netherlands and Ireland. The two databases that provided data for the Netherlands were the GIP database (ambulatory data) and Farminform (hospital data), and for Ireland the Health Service Executive (ambulatory data) and IMS Health (hospital data).

TNFalpha utilisation rates were calculated as a measure of uptake in the health system. The anatomical therapeutic chemical (ATC)/defined daily dose (DDD) methodology was chosen as method for presenting drug utilisation data [24]. The DDD is a dosage measure determined by the World Health Organization (WHO) and is based on the assumed average daily maintenance dose for its main indication use in adults [25]. This common classification system and common unit of measurement to express volume of consumption allows the study of trends in medicines consumption [26]. Utilisation data were obtained for products with ATC codes L04AB01 (etanercept), L04AB02 (infliximab) and L04AB04 (adalimumab) and covered the period 2003–

2007. For infliximab, the DDD is 3.75 mg, for etanercept 7 mg and for adalimumab 2.9 mg. DDDs used in this study are the DDDs for the main indication (RA) and resemble the usual dose for RA as reflected in the current national guidelines (e.g. the DDD of etanercept is 7mg and the usual dose for RA is 50 mg weekly) [25,27]. The data were presented on an aggregated level in DDDs per year or in DDDs per 1000 inhabitants per day. In order to achieve collection of consistent and comparable data, the representative of each participating country was required to provide the data by means of a specially developed, well defined, standardized questionnaire.

### Data analysis

Utilisation rates in DDDs/1000 inhabitants/day 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. For the Netherlands, inpatient data were only available for the years 2006–2008 whereas outpatient data were available for the period 2003–2008. Since the ratio between the in- and outpatient use for 2006–2008 was relative constant (1.65, range 1.59–1.69), this ratio was also used to calculate the missing inpatient use for the years 2003–2005.

Ratios were calculated (with the Netherlands as reference, ratio = 1.00) to express differences in ex-factory prices of similar formulations between countries. Norwegian Kroner (NOK) were converted to euro's using the exchange rate for 2004: 8.3604 and for 2007: 7.8306.

Correlation were estimated for associations between total health expenditure per capita in US\$, purchasing power parity (PPP) and utilisation of TNFalpha inhibitors in DDDs/1000 inhabitants/day between 2003 and 2007 (except for Portugal, data available between 2003 and 2006).

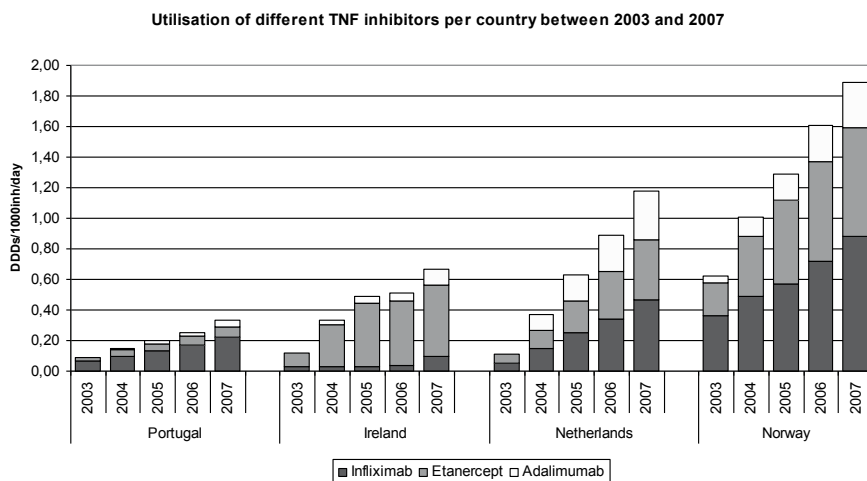
## RESULTS

### Utilisation data

Total national utilisation levels varied between the four countries (Fig. 1). In 2007, utilisation of all TNFalpha inhibitors for all diagnoses ranged from 0.32 DDDs/1000 inhabitants/day for Portugal to 1.89 DDDs/1000 inhabitants/day for Norway. An increase in use over time could be demonstrated for all countries. Ireland had a relative high consumption of etanercept (0.46 DDDs/1000 inhabitants/day for 2007) compared to infliximab and adalimumab (both 0.10 DDDs/1000 inhabitants/day in 2007), but compared to the other countries, a low use of infliximab. Portugal on the other hand, had a relatively high consumption of infliximab. In 2007, the consumption of infliximab was 0.22 DDDs/1000 inhabitants/day versus 0.04 DDDs/1000 inhabitants/day and 0.07 DDDs/1000 inhabitants/day for adalimumab and etanercept, respectively. The Netherlands and Norway had a more or less similar pattern of consumption. In both countries infliximab was the most frequently used TNFalpha inhibitor, closely followed by etanercept and finally adalimumab.

### Regulatory situation

The time lag between marketing authorisation and the market launch in the four countries was limited to several months, see Table 3. Dates of availability of etanercept, adalimumab and infliximab did not differ much between the countries.



**Figure 1** Utilisation of different TNF $\alpha$  inhibitors in Defined Daily Dose/1000 inhabitants/day between 2003 and 2007

### Population and disease characteristics, national health policy characteristics and budgetary constraints

The population characteristics of the four countries are also shown in Table 3. The prevalence of adult RA did not vary much, ranging between 0.49 for the Netherlands to 0.56 cases per 100 inhabitants for Norway.

In all countries the use of infliximab is limited to hospitals because of the intravenous administration route. The decision to start treatment with etanercept and adalimumab is made by the treating rheumatologists but may be continued in the outpatient setting, with the exception of Portugal, where until December 2007 the hospitals were the exclusive centres for TNF $\alpha$  inhibitor therapy. Outpatient distribution of etanercept and adalimumab in Norway and Ireland is solely done by pharmacists in community pharmacies. In the Netherlands, the outpatient distribution is done via two channels; pharmacies and specialised distributions centres. These distributions centres receive the orders through the Internet or via the hospitals whereas the products are delivered by mail or courier service. Patients should have active RA to receive their medication in this manner.

There are minimal varying views of what constitutes appropriate use between the national guidelines for the use of biological disease-modifying antirheumatic drugs (DMARDs) in the treatment of RA. The (current) general consensus among these guidelines is that TNF $\alpha$  inhibitors should be started after 3 months following confirmed diagnosis of RA and failure of treatment with usually one DMARD, mostly methotrexate (MTX; see Table 3).

Between 2003 and 2007, Norway had the highest GDP per capita and spent more money on health care on a per capita basis than Ireland, the Netherlands and Portugal. Collected ex-factory price data for 2004 and 2007 (see Table 3) show a homogenous picture between the four countries. The only exception is adalimumab in Portugal, which is more expensive.

**Table 3** Launch dates and country characteristics (data for 2003 and 2007)

	Norway	the Netherlands	Ireland	Portugal
<b>Population characteristics</b>				
Population (millions)	4.6 - 4.7	16.2 - 16.4	4.0 - 4.3	10.4 - 10.6
Population aged 65 years and over (%)	14.8 - 14.6	13.8 - 14.6	11.1 - 10.8	16.7 - 17.3
<b>Production and expenditure</b>				
GDP per capita in US\$	38294 - 53802	31699 - 39594	34512 - 44381	18789 - 22638
Health expenditure as a share of GDP (%)	10 - 8.9	9.8	7.3 - 7.6	9.7 - 9.9 (a)
THE per capita US\$ PPP	3837 - 4763	3099 - 3837	2521 - 3424	1823 - 2150 (a)
TPE per capita in US\$ PPP	354 - 393	346 - 430 (b)	381 - 609	394 - 489
<b>Disease characteristics [7]</b>				
Prevalence RA (per 100 inhabitants)	0.56	0.46	0.49	0.47
<b>Launch dates</b>				
Infliximab (source: Centocor)	1 June 2000	1 September 1999	20 January 2000	1 October 1999
Etanercept (source: Wyeth)	14-12-2000	15-05-2000	01-08-2000	13-07-2000
Adalimumab (source: Abbott)	Oct 2003	Feb 2004	Dec 2003	Oct 2003
<b>Price information (2004/2007)*</b>				
Infliximab 100mg (vial, solution powder)	0.99/1.01	1.00 (ref)	1.11/n.a.	1.05/0.85
Adalimumab 40mg (prefilled syringe)	0.99/1.09	1.00 (ref)	1.02/1.00	1.79/1.52
Etanercept 25mg (vial, injection powder)	1.06/1.08	1.00 (ref)	0.99/1.04	0.99/0.95
<b>Initiation recommendations [20, 22]</b>				
Trial of DMARD	One DMARD	One DMARD	One DMARD for at least 3 months	At least one DMARD for at least 3 months
Disease activity level required for initiation	Not specified	DAS28>3.2	DAS28>5.1	DAS28 > 3.2 despite treatment with DMARD
<b>Initial reimbursement decision date</b>				
Infliximab	(d)	2001 (e)	(c)	(c)
Etanercept	(d)	01-10-2000	01-07-2000	(c)

Table 3. Continued

	Norway	the Netherlands	Ireland	Portugal
Reimbursement extents (September 2009)				
Inpatient	No co-payment Unrestricted reimbursement	No co-payment Unrestricted reimbursement	No co-payment Reimbursement restrictions is a individual hospital decision	No co-payment. Reimbursement is restricted to certain indications
Outpatient	No co-payment	No co-payment Reimbursement is restricted to certain indications and after failure of at least two DMARDs	Co-payment depends on medical scheme.	No outpatient use (until 2007)

GDP = Gross Domestic Product, THE = Total Health Expenditure, TPE = Total Pharmaceutical Expenditure, DAS = Disease Activity Score, PPP = purchasing power parity, n.a. = not available  
 (a) data for 2003 and 2006

(b) For the Netherlands, no data was available for TPE per capita between 2003 and 2008. TPE per capita for this period was calculated by assuming a linear increase in TPE between 2002 and 2009, for which data was available

(c) Until 2007: hospital only product and products under this classification are not required to undergo a reimbursement process - they can be prescribed in hospital from licensing date  
 (d) The TNFalpha inhibitors are financed through the various Regional Health Authorities (hospitals) since June 1st, 2006

(e) Before 2001 infliximab was a hospital only product and was not required to undergo a reimbursement process. The situation changed due to the insufficient production capacities of etanercept

\* Price information was retrieved from GÖG PPI System 2011. Ratios were calculated (with the Netherlands as reference, ratio = 1,00) to express differences in ex-factory prices of similar formulations between countries

The price of this specific TNFalpha inhibitor may have led to limited access. Reimbursement decision dates do not show a substantial difference between the four countries. Except for Norway, no changes related to reimbursement occurred during the study period. In Norway, as of June 1st, 2006, the use of TNFalpha inhibitors is financed via the Norwegian hospitals. The Norwegian Medicines Agency is not involved in reimbursement decisions. In this way both infliximab and adalimumab/etanercept are paid for from the same hospital budget, but expenses are also covered within the Diagnosis Related Groups (DRG) system, and the drugs have different DRG weights. The system with DRG weights is also different for home based and hospital based medications. Some differences existed in the reimbursement regulations between the countries (September 2009). With the exception of Ireland (co-payment depends on medical scheme), the outpatient use of TNFalpha inhibitors is fully reimbursed provided relevant reimbursement conditions are met. Restrictions are related to specific indications and trial of DMARD. In the Netherlands, TNFalpha inhibitors are fully reimbursed after failure of at least two DMARDs, of which one is MTX. This is in contradiction with the guidelines, where TNFalpha inhibitors may be initiated after failure of one DMARD. In all countries TNFalpha inhibitors were fully reimbursed for inpatient use.

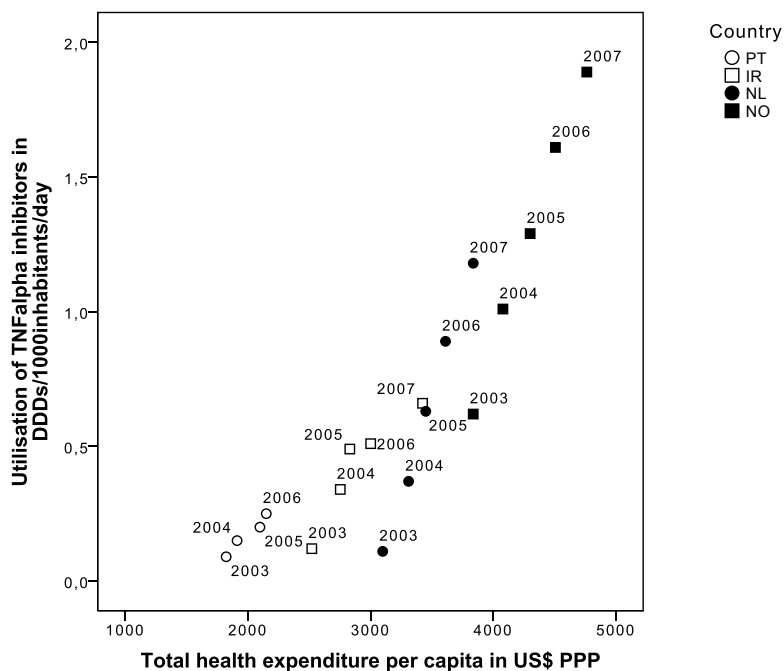
Over time and in all countries treatment of RA has evolved into more intensive strategies (interview data). Biologicals are being prescribed earlier, a shift in the use of DMARDs has occurred and more combination therapy is used on the basis of evidence of clinical efficacy. The increase in the use of TNFalpha inhibitors over time may also be explained by the fact that rheumatologists have become more demanding when it comes to treatment outcomes. Whereas in the past a maximum of 3–4 flares per year was seen as acceptable, nowadays 1 flare per year is considered as such, which can be realized by the use of TNFalpha inhibitors. This explains the increase in use of TNFalpha inhibitors over time but does not explain the differences seen in utilisation between the countries.

Overall, the above mentioned findings do not show unequivocally that system characteristics such as launch dates, guidelines and reimbursement restrictions exert a strong determinative effect on the variation in the level of TNFalpha inhibitor utilisation. Figure 2 shows the overall correlation between the utilisation of TNFalpha inhibitors and health expenditure per capita over time ( $R^2 = 0.81$ ). Virtually the same correlation was found when looking at gross domestic product. Although Norway has a relative low total pharmaceutical expenditure, a strong increase (three fold) was found for the utilisation of TNFalpha inhibitors over time, a pattern also seen for the Netherlands but not for Ireland and Portugal. Figure 3 clearly shows that over time and with the advance of TNFalpha inhibitors as primary line of treatment, the correlation with available health budgets (total health expenditure per capita) becomes more pronounced, approaching 1.0.

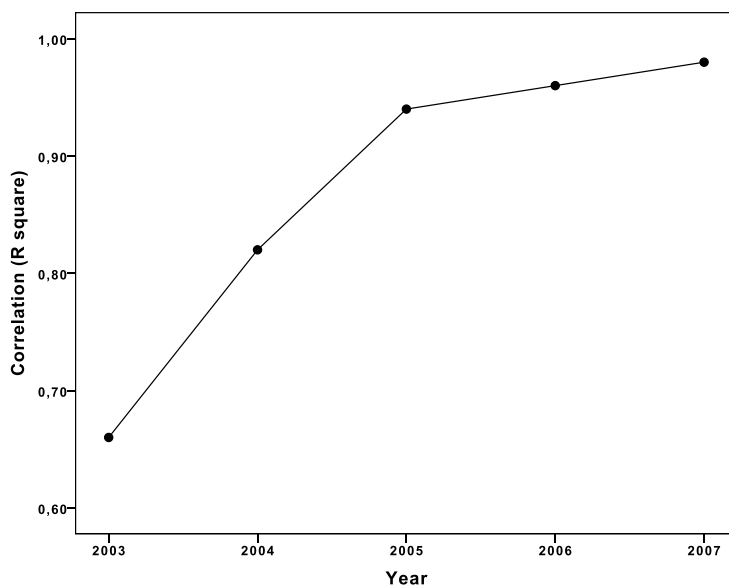
As based on the interviews the following additional observations for the four countries were made:

Portugal has only a limited number of hospitals with rheumatology clinics (in 2007, twelve hospitals). As a consequence access to RA therapy is more difficult for patients living in rural areas, far away from hospitals. In addition, the prescription of TNFalpha inhibitors is restricted to rheumatologists (and internists) in hospitals only (until 2007).





**Figure 2** Utilisation of TNFalpha inhibitors versus total health expenditures per capita between 2003 and 2007. PT = Portugal, IE = Ireland, NL = Netherlands, NO = Norway, PPP = purchasing power parity, DDD = defined daily dose



**Figure 3** Increase in correlation over time

Ireland has no limited access to rheumatologists in hospitals but regional differences in access to treatment in hospitals is seen as the budget spent on TNFalpha inhibitors is an individual hospital decision.

The Netherlands has unrestricted access to rheumatologists. The biggest barrier to TNFalpha treatment is the budget cap for hospitals. Access to outpatient treatment is limited through strict guidelines and reimbursement regulations.

Norway has liberal access to TNFalpha inhibitor treatment. Strategies to control costs of biological agents and to limit prescribing include (i) a central tender system – leading to a cost-based recommendation, (ii) consultation of a colleague before initiating TNFalpha inhibitor treatment in an individual patient and (iii) recommendations for use issued by the Directorate of Health.

Other potential causes of variation in TNFalpha utilisation grouped according to common themes raised during the interviews are shown in Table 4.

## DISCUSSION

This study indicates that there is a large variation in the utilisation of TNFalpha inhibitors between Portugal, the Netherlands, Ireland and Norway. Having approximately the same degree of utilisation in 2003, until 2007 rates tripled in Portugal, increased 6-fold in Ireland and over 10-fold in the Netherlands. The prospect of patients receiving TNFalpha inhibitor treatment therefore depends on the country where they are living. A major driver for the utilisation of TNFalpha inhibitors at the national level seems the country's total health expenditure and national income, as measured by GDP. Explaining this variance in the level of TNFalpha utilisation between the four studied countries should also include factors acting at the level of financing and regulation of the health system, and procedures around reimbursement policies: whether (TNFalpha inhibitor) treatment is being reimbursed. The decision to expand the prescription of TNFalpha inhibitors to rheumatologists in private clinics in Portugal, emphasizes the role of national priority setting (interview data). The interviewed rheumatologists also addressed the importance of health system factors. They stated that a number of other factors, such as access to rheumatologists and levels of recognition of guidelines should also be taken into account when trying to further explain the differences in access to treatment with TNFalpha inhibitors. In addition, this study shows that when TNFalpha utilisation in clinical practice becomes more established, the health expenditures per capita become stronger associated with the total amount used.

This study shows how individual countries are struggling in achieving a balance between equal access to new expensive medicines, such as TNFalpha inhibitors and cost containment which shows the difficulties reconciling the concept of uniform registration and uniform management. The situation in Norway may serve as an example. Consultation of a colleague before initiating a TNFalpha inhibitor in Norway is seen as a valuable tool, as patients have become more demanding and start pushing the rheumatologist to prescribe TNFalpha inhibitors. The above underlines that prescribers of these (new and expensive) medicines should adhere to the guidelines, while regulators and policy makers at the same time should enforce the rules, meaning that non-adherence to guidelines should be discouraged. Options

**Table 4** Possible causes of variation - Clinical culture and attitude towards TNFalpha inhibitor utilisation, according to leading rheumatologists

Factors	Country	Opinions/views
(Non) adherence to guidelines	NL	Adherence to guidelines is high. There is substantial feedback to rheumatologist to avoid inappropriate use
	PT	Adherence to guidelines is low, due to low enforcement and a lack of feedback. Medical internists and to some extent rheumatologists, should be trained and encouraged to adhere more to the guidelines.
Costs of TNFalpha inhibitors in the future	NO	Costs for the treatment of RA will not increase dramatically in the near future. Recent utilisation data have shown a flattening in number of prescriptions for biologicals for rheumatoid arthritis and ankylosing spondylitis.
	PT	Use (and costs) will increase, partly due to a regulatory change in late 2007 and 2008 (see below).
	NL	There is a rapid increase in volume and costs of TNFalpha inhibitors. In 2009, about 250MEUR was spent on TNFalpha inhibitors (both in- and outpatient use).
	IE	There is a pharmaco-economic analysis of all biologics currently licensed in Ireland for inflammatory arthritis ongoing due to the significant budget impact of these drugs
Budgetary and prescription constraints regarding TNFalpha inhibitors	NO	From June 2006, the in- and outpatient use of TNFalpha inhibitors is financed through the hospitals to have the same payer for both infliximab and etanercept/adalimumab.
	PT	From 2008 the prescription of TNFalpha inhibitors is not limited to hospitals anymore. Rheumatologists and internists in private clinics may also prescribe TNFalpha inhibitors. The supporting law should be expressed in the prescription both at hospital and private practice.
	NL	From February 2004 to March 2008, requests for reimbursement of biologics had to be submitted to a subcommittee of an independent foundation National Evaluation of Applications of Drugs (LABAG). Applications for biological therapies for RA could only be submitted by physicians with experience in treating patients with RA. Hospitals receive additional reimbursement for 80% of their expenses on infliximab by insurance companies/government. From January 2012, the in- and outpatient use of all TNFalpha inhibitors will be financed through the hospitals.

IE = Ireland, NL = the Netherlands, PT = Portugal, NO = Norway

for enforcing such rules could include defining quality indicators for treating physicians or administrative requirements before reimbursement (e.g. physician should sign statement that reimbursement restrictions are met).

Some limitations of our data should be noted. The DDD is only a technical expedient and not necessarily equal to the actual use in clinical practice. However, based on the information from the interviews there are no reasons to assume that there were substantial differences in prescribing dosages. In addition, the figure will overrepresent TNFalpha inhibitors usage in RA, as

these biologicals are not prescribed exclusively for RA; although this is the major indication for use so far according to our experts. All interviewed rheumatologists play an active role in their national societies of rheumatology and in the European League Against Rheumatism (EULAR). We therefore feel that they will be able to provide a fair representative view of rheumatologists in their respective countries.

We only looked at the national level and did not take regional and inter-practice variation into consideration. The studies conducted in Australia and the UK show that access to and use of biological treatment may show large regional variability, for example, depending on policy and budget considerations of individual hospitals or insurance companies or the number of rheumatologist in a specific region [9,10]. This was also confirmed for Portugal in our study. The high correlations found in this study are also due to the fact that we used highly aggregated data (causing 'ecological fallacy').

Another limitation is that the data sources used in this study consisted of claims and sales data. Therefore, our results may have been influenced by differences between reimbursement and utilisation within countries or by differences by the location of data collection (public pharmacy, wholesalers or both). Nevertheless, double counting or extrapolation corrections are constant factors within a database and will not influence the trend over time of TNFalpha utilisation as shown. This also indicates that there is a need for a harmonised method of data collection on the utilisation of biologicals within Europe. Unfortunately, data were not available per age category in all countries. Therefore, adjustment for the slight differences in age structure of the four countries (Ireland having the youngest population, Portugal the oldest population) was not done [28]. Finally, the included countries constitute a selection of smaller and medium sized European member states. They differed with respect to their geographical position, GDP and health expenditure thereby providing insights into the extent of variation that exists within Europe (range of total health expenditure per capita (US\$, purchasing power parity) of 20 European countries varied from 1035 US\$ for Poland to 4763 US\$ for Norway (2007)).

In conclusion this study shows that not all European patients do have equal access to important medicines in the treatment of RA. The utilisation of TNFalpha inhibitors is positively correlated with total health expenditure per capita within a country. However, although total health expenditure is seen as the major driver for the differences seen in the utilisation of TNFalpha inhibitors, other factors, acting at the level of financing and regulation of the health system, and issues around reimbursement policies, are also likely to play a role in explaining international variation. In case of evidence-based treatment of RA, the causes of variation should feature prominently on future public health agendas.

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# CHAPTER 3.3

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## VARIABILITY IN MARKET UPTAKE OF PSYCHOTROPIC MEDICINES IN EUROPE REFLECTS CULTURAL DIVERSITY

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## ABSTRACT

Comparative studies on the use of psychotropic medicines show substantial differences between European countries. A widely used argument is that attitudes and beliefs towards psychotropics differ across countries. So far, no studies have looked into the effects of cultural diversity on the use of new psychotropics entering the market. As national cultures relate deeply to held values regarding, among others, what is seen as effective versus ineffective and safe versus dangerous, (cultural) diversity in decision making around the role of new medicines in clinical practice may already be expected from the first day after market authorization (MA).

This study examined the relation between cultural diversity and utilisation of three new psychotropic medicines, namely aripiprazol, duloxetine HCl and pregabalin in Europe. Correlations were calculated between country level sales data up to three years after MA (obtained through IMS Health's MIDAS database and converted to Defined Daily Doses/1000 inhabitants/year) and country-specific scores of cultural dimensions obtained from Hofstede (Power Distance, Individualism, Masculinity, Uncertainty Avoidance, Indulgence and Long-Term Orientation) for 23 European countries. Significant positive correlations were found between Indulgence and total use of the case study medicines at  $t=2$  ( $\rho=0.51$ ,  $p=0.014$ ) and  $t=3$  ( $\rho=0.54$ ,  $p=0.008$ ). A more detailed analysis showed (slight) variation by molecule. No significant correlations were found for the other dimensions.

This study is a first step in including cultural dimensions when explaining cross-national variation in the use of new medicines. It indicates that indulgence is a cultural aspect that relates to the utilisation of three new psychotropics. A country's culture is an important factor and should be considered when performing studies on cross-national variation in medicines use. However, more sustained methods need to be developed or already existing methods should be validated in order to compare the level of medicines use between countries, taking into account the cultural diversity.

## INTRODUCTION

Great differences, as well as startling similarities, can be seen when comparing global cultures. People around the globe are similar in their essential humanity: we communicate with each other, we sustain ourselves with food, and when we sleep we often dream. Yet we speak different languages, eat different foods, and dream different dreams. These are what we call cultural differences [1]. Culture can provide us with many answers on how and why people behave differently around the globe, also in the field of public health and health care [2,3]. Medical care is strongly influenced by cultural norms and values ingrained over hundreds of years. Differences can show up in the types and quantities of medicines doctors prescribe, the kinds and numbers of operations performed, even what blood pressure levels are thought to require treatment [4]. Cultural factors are therefore likely to play a role in explaining international variation in health care use, including utilisation of medicines [5]. Studies have already shown the relevance of cultural diversity in the use of for example antibiotics [6,7]. These studies showed that the cross-national differences in use of antibiotics in ambulatory care are potentially explained by national cultural differences resulting from varying perceptions and influences. Psychotropic medication is another area where differences in medication use across Europe seem to be related to cultural diversity [8,9]. In the last 20-30 years, many international studies have found substantial differences in the use of psychotropic medication between European countries [10,11]. The majority of these studies mentioned an important role for attitudes and beliefs towards psychotropic medication. An international perspective on pediatric psychopharmacology (2008) stated “the cultural context seems to exert a greater influence on the identification and management of psychiatric disorders than on other areas of medicine” [12].

The impact of cultural diversity influencing ‘older’ medication use might be foreseen due to the (relatively) long existence and the embedment of these medicines in clinical practice. But what is the relevance of cultural diversity in explaining cross-national differences in medicines use of medicines that just hit the market? So far, no studies have looked into the effects of cultural diversity on the use of new medicines entering the market. It is well known that new pharmacological therapies are challenging healthcare systems. There is an increasing need to assess their therapeutic value in relation to existing alternatives as well as their potential budget impact [13]. Assessment of the effectiveness compared with alternative treatment(s) already plays an important role in many European member states in determining the reimbursement status of (new) medicines [14]. However, as national cultures relate deeply to held values regarding, among others, what is seen as effective versus ineffective, safe versus dangerous, rational versus irrational and expensive versus inexpensive, (cultural) diversity in decision making around the role of new medicines in clinical practice may already be expected from the first day after market authorization (MA). For the purpose of this study, three new psychotropic medicines that were approved via the EU centralized procedure in 2004, have been selected. These medicines included aripiprazol (Abilify®); duloxetine HCl (Cymbalta®/Xeristar®); and pregabalin (Lyrica®), that are (commonly) used in the treatment of among others schizophrenia, bipolar disorder, anxiety, and major depression [15-17]. These medicines were selected because

despite being clinically relevant for some patients, they are not seen as indisputable medical breakthroughs within their therapeutic areas. Variation in use of these medicines between patients and prescribers, and on a higher level between regions and countries, is therefore likely to be seen due to different cultural approaches in the prescription of these medicines [12,18].

The aim of the study was to assess the relation between cultural diversity and utilisation of these three new medicines in Europe. Developments over time were studied (up to three years after MA) to see whether the effect of cultural diversity varied following the settlement of the new medicines on the European market.

## THEORETICAL BACKGROUND

### **Cultural dimensions and expectations towards use of aripiprazol, duloxetine HCl and pregabalin in EU member states**

The effect of cultural dimensions is complex. It influences a multitude of social phenomena on the macro, such as patterned relations between large social groups, and micro level, e.g. the behavior of individualistic members of the society. The dynamic nature of culture conveys the top-down–bottom-up processes where one cultural level affects changes in other levels of culture [19]. Macro-level systems appear increasingly likely to influence the nature of micro-level interaction. Reciprocally, behavioral changes at the individual level, through bottom-up processes, become shared behavioral norms and values, modifying the culture of a macro level entity [19,20]. Coleman's scheme of the micro-macro linkage is one of the most useful expository vehicles for thinking about multi-level issues in social science research [20]. The diagram indicates the relationship between macro factors (e.g. institutions) and the micro factors that underlie their causal relation (values, economic behavior). Most of the research on culture has focused on identifying the core cultural values that differentiate cultures on a macro level. An example of a popular and validated approach is Hofstede's model of cultural dimensions [21]. He distinguished six dimensions along which cultural values can be compared with other cultures: individualism–collectivism; uncertainty avoidance; power distance (strength of social hierarchy); masculinity–femininity (task orientation versus person-orientation); long term–short term orientation and indulgence–restraint (see box 1) [22]. As Hofstede operationalized the concept of culture into quantifiable measures, it can be used in cross-national country comparative studies [6,7].

Based on Hofstede's model of cultural dimensions, we expect the following effect of these cultural dimensions on the use of aripiprazol, duloxetine HCl and pregabalin.

Power distance refers to 'preferences of how persons with a different (social) status communicate with each other'. Albeit patient empowerment is a topic of interest in current health care, the asymmetry between doctors and patients remains persistent [23]. Still countries differ in their power distance and Deschepper et al. (2008) showed that power distance was positively correlated to the use of antibiotics [6]. They stated that in countries with a low power distance, a preference for deliberation about the use and sense of antibiotics between patients and doctors might affect the prescription of antibiotics [6]. Furthermore, low country scores on Power Distance may have implications for collaboration between doctors and other health

**Box 1. Hofstede's definitions for the six cultural dimensions (adapted from <http://geert-hofstede.com/dimensions.html>)**

**Power distance (PDI)** relates to the extent to which the less powerful members of a society accept and expect that power is distributed unequally. It suggests that a society's level of inequality is endorsed by the followers as much as by the leaders [7].

**Individualism (versus collectivism) (IDV)** A society's position on this dimension is reflected in whether people's self-image is defined in terms of "I" (individualism) or "we" (collectivism).

**Masculinity (versus femininity) (MAS)** refers to the distribution of emotional roles between the genders. The masculinity side of this dimension represents a preference in society for achievement, heroism, assertiveness and material reward for success. Society at large is more competitive.

**Uncertainty avoidance (UAI)** indicates the degree to which the members of a society feel uncomfortable with uncertainty and ambiguity, and shows how comfortable society is in unstructured situations that are novel, unknown and surprising.

**Long-term (versus short-term orientation) (LTO)** fosters pragmatic virtues oriented towards future rewards, in particular saving, persistence and adaptation to changing conditions.

**Indulgence (versus restraint) (IVR)** Indulgence stands for a society that allows relatively free gratification of basic and natural human drives related to enjoying life and having fun.

care professionals, resulting in exchange of information about (optimal) medicines therapy. This same phenomenon can be expected to occur with the utilisation of other medicines. A preference for discussion about the use and sense of new CNS medications might be favored in countries with a low power distance leading to lower use as contrasted with a 'doctor knows best' attitude in countries scoring high for power distance.

Individualism has to do with 'the degree to which individuals are integrated into groups or not'. Previous literature indicates that people from individualist cultures are more likely to tolerate diversity and deviation from the norm because such cultures are extremely fragmented, with extensive individuality, due to the desirability of personal goals [21,24,25]. Diseases interfering with the CNS are more likely to cause behavior deviated from the norm. In individualistic countries CNS patients may be less stigmatized and access to appropriate services and/or use of CNS medication might be more common [24].

Masculinity can be defined as 'the distribution of emotional roles between the genders' and is expected to have contradictory effects on the use of these three medicines. On the one hand, countries with a masculine culture may be expected to correlate negatively with the use of CNS medications, e.g. because these countries value a live to work ethic 'boys don't cry' mentality. On the other hand, these countries are strongly result oriented which hypothetically may lead to a quicker initiation of treatment in order to overcome negative effects of the disease of the CNS and thus to a higher level of use.

Uncertainty avoidance has to do with ‘a society’s tolerance for uncertainty and ambiguity’. In countries with high uncertainty avoidance more CNS medications may be used because doctors may try to avoid the ambiguity in cases of severe CNS disorders. However, because these are new medicines related to uncertainty and ambiguity with regard to effectiveness, long term side effects, and/or cost, doctors and patients might be less willing to use these medicines compared to older, more commonly used medicines in countries with a strong uncertainty avoidance. However, it should be kept in mind that uncertainties about the effectiveness of those medicines may also exist.

Long-term orientation indicates the extent to which a society focuses on the future instead of the present only. Countries with a short-term orientation are normative in their thinking but also have a focus on achieving quick results whereas societies with a long term orientation show perseverance in achieving results. In addition, countries with a short term orientation may adapt to changes, such as the introduction of new medicines, more rapidly than countries with a long term orientation, resulting in a higher use of these new CNS medications.

Indulgence is the feature of a society that allows satisfying, relatively free, certain feelings and desires. The opposite is restraint which stands for a society that ‘suppresses gratification of needs and regulates it by means of strict social norms’ [21]. Indulgence can be expected to relate positively with the use of CNS medications, as these medicines may have a rewarding effect on patients and the incentive of discontinuation might therefore be lacking. Countries with a high level of restraint might suppress the use of these new medicines, either due to the higher treatment costs associated with the use of these medicines and/or little additional therapeutic value or due to the risk of dependence.

Based on these hypotheses we expect that power distance, individualism, long-term orientation and indulgence may be correlated with the consumption of aripiprazol, duloxetine HCl and pregabalin. For a summary of the hypotheses, see table 1.

## Methodology

### Data source

IMS Health’s MIDAS database has been used as the source of all sales data for aripiprazol, duloxetine HCl and pregabalin from the market authorization date in 2004 until December 2009. MIDAS is a summary of data obtained from IMS Health’s detailed audits of pharmaceutical purchases made by retailers (in 70 countries) and hospitals (in 45 countries). MIDAS contains

**Table 1** Summary of hypotheses

Hofstede dimensions of national culture	Hypothesized to be:
Power distance	Positively associated with the use of the case study medicines
Individualism (versus collectivism)	Positively associated with the use of the case study medicines
Masculinity (versus femininity)	No effect on the use of the case study medicines
Uncertainty avoidance	No effect on the use of the case study medicines
Long-term orientation (versus short-term)	Negatively associated with the use of the case study medicines
Indulgence (versus restraint)	Positively associated with the use of the case study medicines

information on sales of individual products, measured in both currency and physical units, as well as information on the product manufacturer, active ingredient, brand, form, strength, pack size, and therapeutic class.

Data used in this analysis cover sales to the retail pharmacy sector. Sales data include direct sales by suppliers to pharmacies and indirect sales via wholesalers. The retail pharmacy sector accounts for most sales in all of the countries considered in the analysis. Data were obtained for all EU member states (per 01/05/2004), except for the Mediterranean islands of Malta and Cyprus.

Data on cultural dimensions were obtained from Hofstede [21]. Putting together national scores (from 1 for the lowest to 112 for the highest), Hofstede's model allows international comparison between cultures using six factors of value difference between cultures (see box 1) [22]. The country scores on the dimensions are relative and can be assessed from: <http://www.geerthofstede.nl/dimension-data-matrix>. These dimensions have been replicated in a number of successive studies by different researchers using a variety of other matched samples of respondents [26]. Both studies that have assessed the relevance of cultural characteristics in explaining variation in the use of antibiotics, have used Hofstede's theory of cultural dimensions. These dimensions furthermore provide a relatively general framework for analysis that can be easily applied because it reduces the complexities of culture and its interactions into quantifiable dimensions [7]. Country scores for Hofstede dimensions as presented in 'Cultures and Organizations 3rd edition 2010' were available for all countries for which IMS provided utilisation data [27].

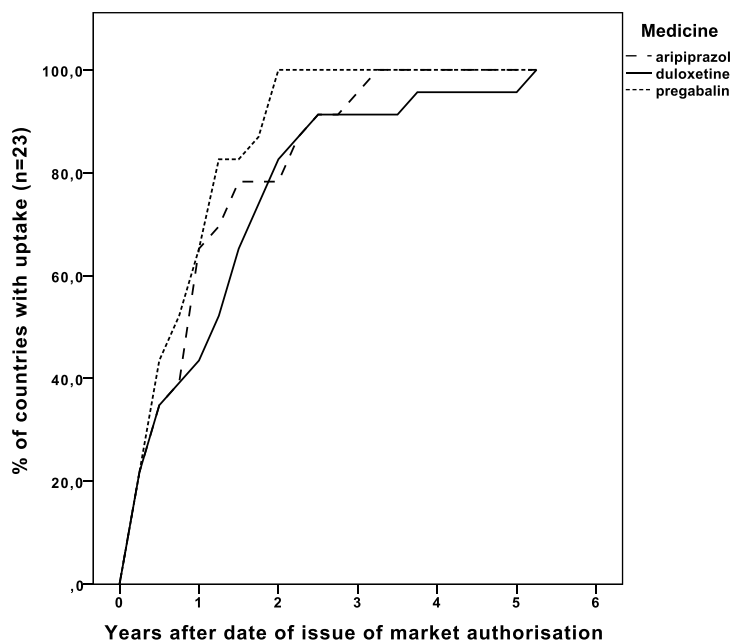
#### *Data measurement*

Volume was used as the measure of consumption and was expressed in the World Health Organization defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a medicine used for its main indication in adults [28]. To allow for different population sizes, volume was expressed per 1000 inhabitants. Volume data were obtained on a quarterly level. Population statistics on number of inhabitants were obtained from the website of the United Nations, Department of Economic and Social Affairs for 2009 [29].

#### *Data analysis*

For each quarter following the date of market authorization, it was assessed how many countries showed an uptake of aripiprazol, duloxetine HCl or pregabalin. Uptake was present if the level of use was higher than 0.01 DDDs/1000inhabitants/day (arbitrary cut off point). The percentage of countries with adoption of the new medicine could then be calculated and reflected in the adoption curve as shown in figure 1.

Spearman correlation coefficient rho was used to calculate correlations between the total usage level of aripiprazol, duloxetine HCl and pregabalin per country at various moments in time and country scores of Hofstede dimensions. Usage level was defined as the level of utilisation in DDDs/1000inhabitants/day in a certain quarter and year. A p-value of 0.05 or smaller was considered significant. To limit the influence of possible national system level factors, such as differences in time to reimbursement decision or national decisions about the uptake of the new medicines in clinical guidelines,  $t=0$  was set country specific. In other words,  $t=0$  was set



**Figure 1** Adoption curve of the three medicines included in the present study

at the moment the first usage was seen in a country. Stratified analyses were conducted by studying each molecule separately. As utilisation of medicines is known to vary with national wealth as expressed by gross domestic product (GDP), potential effects were examined by calculating the partial correlations controlled for GDP per capita and then compared with the non-controlled correlations.

## RESULTS

Consumption of the case study medicines was seen in all countries. One year after uptake, total utilisation of aripiprazol, duloxetine HCl and pregabalin ranged between 0.4 and 344.2 DDDs/1000inhabitants/year (Poland and Spain, respectively). This increased to range 19.0-562.1 DDDs/1000inhabitants/year (Poland and Spain, respectively), three years after uptake (see table 2). In general, pregabalin was used more often than aripiprazol and duloxetine (see figure 2). The adoption curve (see figure 1) shows a similar pattern for all three molecules with pregabalin having a slightly faster adoption compared to the other two medicines. This similarity in pattern reflects the homogeneity of the three molecules, i.e. 2 years after market authorization, approximately 80% of all countries have reported use of all three molecules.

Variations can be seen between the level of usage over time for the various EU member states (table 2). Both Spain and France had a relatively high level of use, one year after uptake. After three years of uptake, Spain remained to have a relatively high level of use, closely followed



**Table 2** Total use of the 3 selected medicines and country scores on Hofstede dimensions

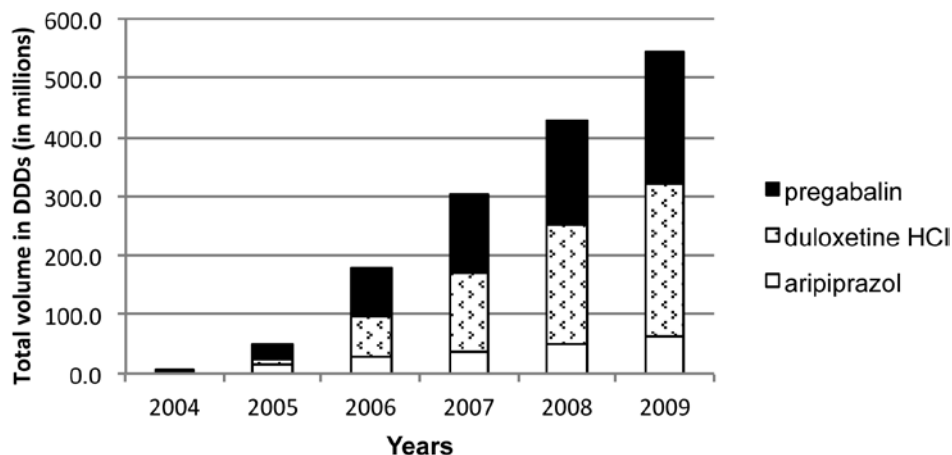
Country	Total use of the 3 selected medicines in DDDs/1000inhabitants/year				Country scores					
	t=0	t=1	t=2	t=3	PDI	IDV	MAS	UAI	LTO	IVR
Austria	8.9	52.0	101.6	214.5	11	55	79	70	60	63
Belgium	4.0	253.4	426.6	506.1	65	75	54	94	82	57
Czech Republic	0.5	30.7	53.6	56.5	57	58	57	74	70	29
Denmark	26.8	146.1	232.2	341.2	18	74	16	23	35	70
Estonia	10.9	33.7	52.3	45.7	40	60	30	60	82	16
Finland	2.9	123.5	269.7	452.3	33	63	26	59	38	57
France	46.0	230.9	184.8	239.9	68	71	43	86	63	48
Germany	3.8	133.7	201.9	262.3	35	67	66	65	83	40
Greece	13.9	142.4	332.3	494.9	60	35	57	112	45	50
Hungary	5.1	80.4	118.2	169.8	46	80	88	82	58	31
Ireland	8.8	152.4	254.5	350.7	28	70	68	35	24	65
Italy	6.8	127.4	203.6	262.9	50	76	70	75	61	30
Latvia	2.3	31.2	51.0	48.4	44	70	9	63	69	13
Lithuania	1.2	59.1	101.3	92.7	42	60	19	65	82	16
Luxembourg	11.0	226.1	353.2	455.2	40	60	50	70	64	56
Netherlands	5.4	91.5	138.5	176.1	38	80	14	53	67	68
Poland	0.0	0.4	10.2	19.0	68	60	64	93	38	29
Portugal	3.4	181.4	340.5	440.5	63	27	31	104	28	33
Slovak Republic	3.2	58.2	96.20	140.8	104	52	110	51	77	28
Slovenia	2.5	158.3	282.9	356.3	71	27	19	88	49	48
Spain	41.5	344.2	464.2	562.1	57	51	42	86	48	44
Sweden	0.9	76.5	202.7	336.1	31	71	5	29	53	78
United Kingdom	2.4	78.7	141.7	184.7	35	89	66	35	51	69

PDI = power distance, IDV = individualism, MAS = masculinity, UAI = uncertainty avoidance, LTO = long-term orientation, IVR = indulgence

by Belgium, which had a relatively low consumption one year after market uptake. This same pattern can be seen for a country like Portugal, and to a lesser extent Greece.

Country scores on the Hofstede dimensions clearly varied across all countries (table 2). Of all dimensions, masculinity was found to have the largest range (5-110) and long-term orientation the lowest range (24-83) between the studied countries. Correlations between Hofstede dimensions individualism, long-term orientation and indulgence and total use of aripiprazol, duloxetine HCl and pregabalin tended to become stronger over time, but they were only statistically significant for indulgence at t=2 ( $\rho=0.51$ ,  $p=0.014$ ) and t=3 ( $\rho=0.54$ ,  $p=0.008$ ), see table 3. When controlling the correlations between Hofstede dimensions and the total use of aripiprazol, duloxetine HCl and pregabalin for wealth, Hofstede dimension indulgence remained significant (data not shown).

A more detailed analysis showed (slight) variation by molecule (see figure 3a-c). Stratified analysis revealed positive significant correlations for indulgence (at t=1, 2 and 3) and a negative



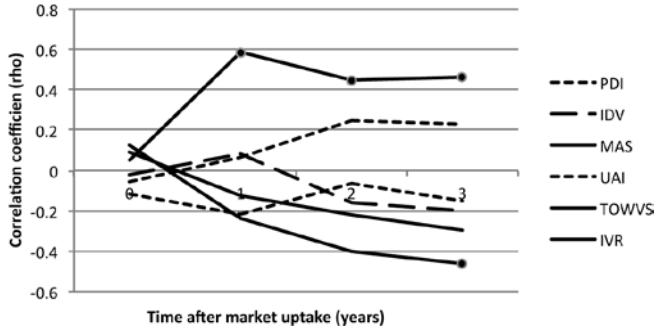
**Figure 2** Total volume of aripiprazol, duloxetine HCl and pregabalin, 2004 -2009. Source: MIDAS database, IMS Health, 2004 – 2009. The year 2004 only includes quarter 3 and quarter 4

**Table 3** Correlations between the total use of aripiprazol, duloxetine HCl and pregabalin and Hofstede dimensions

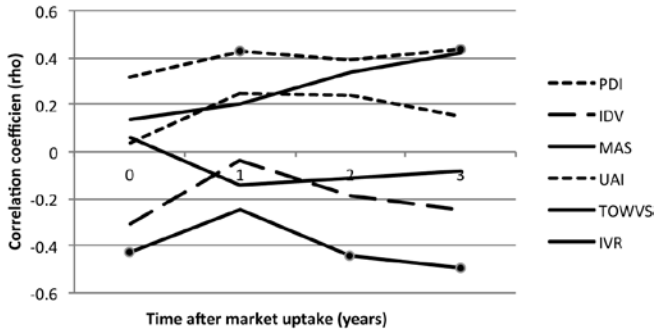
Cultural dimensions	Spearman correlation coefficient (Rho) (p-value)			
	t=0	t=1	t=2	t=3
PDI	0.122 (0.580)	.144 (.511)	.019 (.930)	-.024 (.914)
IDV	0.018 (0.934)	-.022 (.920)	-.135 (.540)	-.170 (.439)
MAS	0.120 (.587)	-.078 (.725)	-.106 (.629)	-.086 (.696)
UAI	.106 (.631)	.319 (.137)	.286 (.186)	.265 (.222)
LTO	-.125 (.569)	-.267 (.219)	-.392 (.064)	-.407 (.054)
IVR	.266 (.221)	.406 (.055)	.505* (.014)	.542* (.008)

PDI = power distance, IDV = individualism, MAS = masculinity, UAI = uncertainty avoidance, LTO = long-term orientation, IVR = indulgence, \* = statistically significant

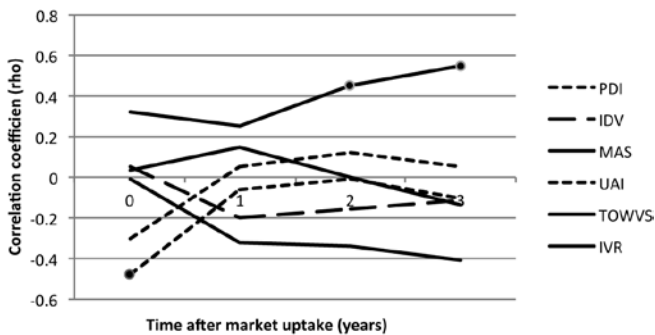
significant correlation for long term orientation at t=3 with the use of aripiprazol. Furthermore, negative significant correlations were found for long term orientation (at t=0, 2 and 3) with the use of duloxetine HCl and a positive significant correlation at t=1 and t=3 for uncertainty avoidance. Positive significant correlations were also found for pregabalin and the cultural dimension indulgence at t=2 and 3 and a negative significant correlation was found at t=0 for power distance and the use of pregabalin. Long term orientation was found to correlate most strongly (negative) with the use of all case study medicines (although not always significant). Indulgence was found to have the highest positive correlation for both aripiprazol and



**Figure 3a** Correlations between aripiprazol and Hofstede dimensions over time. Marked dots show statistically significant correlations. Abbreviations: PDI = power distance, IDV = Individualism, MAS = masculinity, UAI = uncertainty avoidance, LTO = long-term orientation, IVR = indulgence



**Figure 3b** Correlations between duloxetine HCl and Hofstede dimensions over time. Marked dots show statistically significant correlations. Abbreviations: PDI = power distance, IDV = Individualism, MAS = masculinity, UAI = uncertainty avoidance, LTO = long-term orientation, IVR = indulgence



**Figure 3c** Correlations between pregabalin and Hofstede dimensions over time. Marked dots show statistically significant correlations. Abbreviations: PDI = power distance, IDV = Individualism, MAS = masculinity, UAI = uncertainty avoidance, LTO = long-term orientation, IVR = indulgence

pregabalin, but not for duloxetine HCl. Over time most of Hofstede dimensions correlated only slightly with the three case study medicines. Especially in the case of pregabalin, most correlation trends over time tend off to zero.

## DISCUSSION

This study assessed the relation between cultural diversity and utilisation of three new psychotropic medicines in Europe. Developments over time were studied (up to three years) to explore whether the effect of cultural diversity on the total use of these new medicines varied following the settlement of these medicines on the European market.

Although homogeneity in the uptake (availability) was seen between the three molecules, large cross-national variation was seen in the level of use between one and three years after the first date of usage seen in a country. This variation came not as a surprise as many previous studies have shown consistent significant cross-national variation in older psychotropic medicines utilisation [8-11]. However, none of these studies linked cultural diversity to the level of use of the medicines included in the studies.

The findings of a positive correlation for CNS medication use with indulgence corroborates with our hypothesis with regard to this dimension and do show that (although limited) cultural diversity plays a role in the level of use of the case study medicines. If we apply indulgence to medical situation and decision making, policy makers and/or physicians may suppress the use of new medicines, especially when treatment costs are higher compared to the already existing options and positive effects may vary between different patients. Criteria for cost-effectiveness are used for reimbursement decision in most European countries [30]. The dimension long term orientation showed a negative trend as hypothesized. Relevant elements of short term orientated societies; social consumption, spending and immediate gratification of needs expected, do seem to exert a role in the consumption of new medicines [21]. However, the correlations were not found to be significant. The trends for Hofstede dimensions power distance and masculinity started positive, but trend off to zero. DeSchepper et al. (2008) showed that power distance was positive correlated with the use of antibiotics suggesting that the cultural-specific way people deal with authority is an important factor in explaining cross-national differences in antibiotics use [6]. Perhaps, due to the newness of these medicines, cultural diversity in power distance has not yet shown to have an effect on the use new medicines. Finally our hypothesis was confirmed for Hofstede dimension uncertainty avoidance but not confirmed for Hofstede dimension Individualism. The (slight) variation between the three case study medicines furthermore shows the importance of stratified analyses. After all, when developing specific policies, it may be important to know which cultural dimension may play a role in the utilisation of the medicine.

This study has some limitations. The number of countries is (still) limited and the study may therefore be underpowered to detect significant differences between countries. Whether the results found in this study may be due to the fact that cultural diversity does not play an important role in explaining cross-national variation in new psychotropic medicines use, or that

Hofstede's model is unsuitable for new medicines just entering the market remains unanswered. Hofstede's model is the model most validated by research, based on rigorous cultural research (rather than on somebody's opinion) [31]. It is also the most widely cited model in existence and his observations and analyses provide researchers with a highly valuable insight into the dynamics of cross-cultural diversity [31]. The model however, has not been without criticism, notably by Bhimani (1999), Harrison & McKinnon, (1999) and McSweeney (2002) [32-34]. Critiques of Hofstede's model are mainly related to the quantitative nature of his research. For the purpose of this study, the key critique comes from Smith (2002) who argues that "...if we compare culture A and culture B on some attribute, the mean scores (macro level) that we achieve will tell us nothing about variability within each nation, nor will it tell us whether the particular individuals (micro level) whom we sampled are typical or atypical of that culture" [35].

Besides cultural values, other determinants play a role when explaining variation in medicines use such as access to specialists, level of co-payment and moment of reimbursement decisions and outcomes of these decisions [5]. To limit the possible effect of the moment of reimbursement decision we set  $t=0$  at the moment the first usage was seen in a country. As these medicines were approved via the EU centralized procedure, no differences in market authorization dates could exist between the various countries. Unfortunately, other determinants are not (easily) measurable or available. Our limited sample size and use of a nonparametric approach precluded the possibility of a more fine-grained analysis involving other/multiple values.

Cultural dimensions may be the result of other important factors, such as the country's wealth. However, when controlling the correlations between Hofstede dimensions and the total use of aripiprazol, duloxetine HCl and pregabalin for wealth, Hofstede dimension indulgence remained significant.

Despite these limitations, we do believe that cultural dimensions as presented by Hofstede are a (simple but) useful tool to measure the extremely complex concept of culture and that they may offer an opportunity to improve our understanding of the remarkable and partially unexplained cross-national variation in medicines use, even for medicines just entering the market. After all, the strength of cultural dimensions is that they are the resultant of many interacting factors, that they can put phenomena together that initially seem unconnected and change slowly over the course of generations [6]. A country's culture is an important factor within a health care system and should also be considered when explaining cross-national variation in the use of new medicines. After all, culture affects the behavior of members of a country and benchmarking the level of medicines use against a country with a dissimilar culture may be ineffective

Nevertheless more cross-national comparative research, and the availability of larger data sets including data on an individual level, is needed to better understand the relationship between cultural diversity and the use of (new) medicines. After all, policy is never made in a 'cultural vacuum': one cannot simply transplant a policy measure from one country to another without paying attention to cultural aspects. Furthermore, the chance of (new) policies being implemented is more likely when there is sufficient base of public support.

In conclusion, this study is a first step in including cultural dimensions when explaining cross-national variation in the use of new medicines. Although only slightly, it indicates

that indulgence is a cultural aspect that relates to the utilisation of three new psychotropic medicines, suggesting that lower regulation by means of strict social norms is a main factor in explaining cross-national variation between these medicines.

## ACKNOWLEDGEMENTS

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# CHAPTER 3.4

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## **WAITING FOR REIMBURSEMENT? – PATIENT ACCESS TO THREE NEW PSYCHOTROPIC MEDICINES IN EUROPE**

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*Submitted for publication*

# ABSTRACT

## Introduction

In 2004, three new psychotropic medicines, aripiprazol, duloxetine HCl and pregabalin, were granted a market authorization (MA) via the European Union (EU) centralized procedure.

This research focused on variation in the duration and outcome of national reimbursement decisions and their implications for patient access to these medicines in Europe supported by 5 years consumption data.

## Methods

Country level consumption data (January 2004 – December 2009) were obtained through IMS Health's MIDAS database for 19 EU countries. Information on national reimbursement decisions was obtained through the European network for Health Technology Assessment.

Time from market authorization to the reimbursement decision was calculated for each country and molecule separately. Scatterplots were constructed to visualize the distribution of the countries according to the level of medicines use (5 years after MA) and the time to the reimbursement decision.

## Results

Consumption of the case study medicines was seen in all countries, except for duloxetine HCl in Poland. The level of medicines use (5 years after MA) ranged from 13.1 – 102.0 DDDs/1000inhabitants/year for aripiprazol, from 0.0 – 401.6 DDDs/1000inhabitants/year for duloxetine HCl and from 0.66 – 465.9 DDDs/1000inhabitants/year for pregabalin. All medicines received a positive reimbursement decision on a national level in 17 of the 19 countries. Median time from MA to reimbursement ranged from 6.3 – 14.9 months for aripiprazol, from 9.5 – 18.4 months for duloxetine HCl and from 6.9 – 20.8 months for pregabalin. Scatterplots and calculated  $R^2$ -values (0.2 for aripiprazol, 0.04 for duloxetine HCl and 0.3 for pregabalin) suggest a weak to moderate relation between the level of use (5 years after MA) and the time to reimbursement decision.

## Conclusion

This study showed cross-national variation in the level of use of the case study medicines (5 years after MA) and reimbursement decisions. Time to reimbursement was weakly to moderately related to the level of medicines use, even 5 years after market authorization. When explaining causes of cross-national variation in medicines use, the effects of the (speed of) reimbursement decision should be taken into account.

## INTRODUCTION

In 2004, three new psychotropic medicines were granted a market authorization (MA) via the European Union (EU) centralized procedure: aripiprazol (Abilify®), duloxetine HCl (Cymbalta®, Xeristar®) and pregabalin (Lyrica®). Aripiprazol is an atypical antipsychotic and antidepressant that is used in the treatment of schizophrenia, bipolar disorder and clinical depression [1]. Duloxetine HCl, is a serotonin-norepinephrine reuptake inhibitor that is licensed for the treatment of major depression, diabetic neuropathies and major anxiety disorder [2]. Pregabalin, a gamma-aminobutyric acid (GABA) analogue with antiepileptic, analgesic and anxiolytic activity is indicated for the treatment of neuropathic pain, anxiety disorders and may be used as an adjunct therapy for partial seizures with or without secondary generalization in adults [3]. Authorization details on aripiprazol, duloxetine HCl and pregabalin are presented in table 1. Evidence for the benefit/risk assessments of these medicines was mostly obtained through studies that compared the effect of the new medicine with a placebo, as comparative trials with other medicines were (often) lacking [1-3]. Tolerability profiles did not identify any unexpected or serious adverse reactions that would create special concern and were stated as acceptable. Based on the favorable benefit/risk assessments, these three medicines were granted a market authorization.

In the period following market authorization, expert and public opinions have been presented about the (limited) added value of these medicines in clinical practice. A review of aripiprazol in the treatment of patients with schizophrenia or bipolar I disorder by Citrome et al. (2006) stated that the overall favorable tolerability profile of aripiprazol makes it an attractive option for the treatment of both schizophrenia and bipolar disorder [4]. However, many other studies included in this review addressed the difficulty in seeing clinical advantages for new antipsychotics that, on the whole, are not so different from their predecessors when compared among groups of patients [4]. Examples of independent negative advice regarding the use of these medicines comes from for example Prescrire International; a non-profit continuing education organisation committed to better patient care [5]. They stated “pregabalin, an antiepileptic drug, now approved for the treatment of “general anxiety”, offers no advantage. General anxiety requires psychological treatment first of all and sometimes calls for the use of tranquilisers (benzodiazepines).” Furthermore they stated “in the field of psychotropic drugs,

**Table 1** Characteristics of the medicines included in this study

International Nonproprietary Name	Brand name	Therapeutic area	WHO ATC code	Market Authorisation date
aripiprazol	Abilify®	Schizophrenia Bipolar Disorder	N05AX12	04/06/2004
duloxetine HCl	Cymbalta®, Xeristar®	Diabetic Neuropathies, Depressive Disorder	N06AX21	17/12/2004
pregabalin	Lyrica®	Anxiety Disorders, Epilepsy Neuralgia	N03AX16	06/07/2004

the new drugs offer patients precious few benefits” [6,7]. Prescrire’s 2009 drug review even stated to avoid duloxetine HCl, regardless of the condition, because of serious side effects, and aripiprazol should not be used in adolescent schizophrenia (over 15 years of age) as it has not shown to be more effective than haloperidol [8]. Despite these criticisms, aripiprazol has become quite popular and is the fifth best selling prescription medicine in the US in 2011 [9].

It may be clear from above that despite being clinically relevant for some patients, they are not seen as indisputable medical breakthroughs within their therapeutic areas. Variation in use of these medicines between patients and prescribers, and on a higher level between regions and countries, is likely to occur. After all, the prescribing and use of these medicines will heavily depend on the individual opinion of prescribers and users. Variation might also be seen in policy decision making around these medicines, such as the decision whether or not to reimburse the new medicine and under what condition. In the end, policy decision making is the result of a combination of scientific evidence and (clinical) opinions [10]. Despite the harmonization of the evaluation of new medicinal products entering the market, true access and availability of medicines is far from being harmonized because pricing and reimbursement policies are still matters for individual member states to consider and depend on their government policies, health resources, public health system and expert and public opinions [11-15]. Decision makers may have different considerations when deciding about the reimbursement of these medicines. Even if a positive decision is made, restrictions for reimbursement, level of reimbursement, and the time taken to the reimbursement decision may have an effect on the uptake and level of use of these medicines [16]. Especially with respect to these three medicines, these issues may likely play an important role as the clinical relevance or clinical need of these medicines seems to be questionable. The emphasis of our research is on cross-national variation in the duration and outcome of reimbursement decisions and their implications for patient access to new psychotropic medicines in European member states supported by 5 years consumption data of these three medicines.

## METHODOLOGY

### Data sources

IMS Health’s MIDAS database has been used as the source of all sales data for aripiprazol, duloxetine HCl and pregabalin from the market authorization date in 2004 until December 2009 (=5 years after market authorization). MIDAS is a summary of data obtained from IMS Health’s detailed audits of pharmaceutical purchases made by retailers (in 70 countries) and hospitals (in 45 countries). MIDAS contains information on sales of individual products, measured in both currency and physical units, as well as information on the product manufacturer, active ingredient, brand, form, strength, pack size, and therapeutic class. The data used in this analysis cover sales to the retail pharmacy sector. Sales data include direct sales by suppliers to pharmacies and indirect sales via wholesalers. The retail pharmacy sector accounts for most sales in all of the countries considered in the analysis.

Data used for this study were obtained for all EU member states per 01/05/2004, except for the Mediterranean islands of Malta and Cyprus.

**Box 1. Questions addressed to EUnetHTA partners.**

1. Is the pharmaceutical reimbursed/funded?
2. Since which date is the pharmaceutical reimbursed/funded (please specify at least month and year)? (please include the source in which you could find these data)
3. For which indication is the pharmaceutical reimbursed/funded?
4. Are there any special circumstances (e.g restrictions or organisational issues) regarding the reimbursement/funding of the pharmaceutical?
5. Was there a co-payment for the pharmaceutical in the year of the reimbursement decision? If yes, what was the co-payment?

Information on national reimbursement decisions was obtained through the European network for Health Technology Assessment (EUnetHTA) [15]. EUnetHTA is a network of government appointed organisations that produce or contribute to HTA in various European countries and member states. Twenty EUnetHTA partners (one partner per EU member state included in the analysis), including national institutes of public health, health authorities or health insurance board, were sent a semi structured questionnaire (month of issue: April 2012) by email which included five questions regarding the three molecules included in this study (see box 1). Partners not responding within two weeks were sent a reminder. The following countries were included: Austria, Belgium, the Czech Republic, Denmark, Estonia, Finland, France, Hungary, Italy, Latvia, Luxembourg, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom (England/Wales).

**Data measurement**

Volume was used as the measure of consumption and was expressed in the World Health Organization defined daily dose (DDD) [18]. To allow for different population sizes, volume was expressed per 1000 inhabitants. Volume data were obtained on a quarterly level. Population statistics were obtained from the website of the United Nations, Department of Economic and Social Affairs [19].

A medicine was defined as available if consumption was over 0.00 DDDs/1000 inhabitants/year in a certain quarter between January 1, 2004 and December 31, 2009. The date where first usage was seen was defined as 'first usage date'.

**Data analysis**

Time from market authorization to the first decision on reimbursement and time between market authorization and first usage date was calculated for each country (for which data was available) and molecule separately. With this information, the time between the reimbursement decision date and the first usage date for the various countries and molecules could be calculated. In addition, aggregated median times were presented for each molecule. All times were presented in months.

For each molecule (and per country) usage patterns over time, including the moment of reimbursement decision were plotted. In addition, for each molecule scatterplots, including the correlation coefficient R-squared, were constructed to visualize the distribution of the countries according to the level of medicines use (5 years after MA) and the time to the first reimbursement decision. Based on the information received through the EUnetHTA partners, the number of restrictions were counted and clustered into two groups. Countries with ‘no restriction’ or the restriction that reimbursement was limited to the indication as mentioned in the Summary of Product Characteristics (SPC) were assigned to group 1 (number of restrictions  $\leq 1$ ). Countries with more than one restriction or one restriction other than that reimbursement was limited to the indication as mentioned in the SPC, were assigned to group 2 (number of restrictions  $\geq 2$ ). The Mann–Whitney U test was used for assessing whether the distribution of the level of medicines use (5 years after MA) was similar across these two groups.

Finally, for each molecule, scatterplots, including the correlation coefficient R-squared, were drawn to visualize the distribution of the countries according to the number of restrictions and the time taken to the first reimbursement decision.

## RESULTS

Out of the 20 EUnetHTA partners that were approached, all countries except Ireland (19 EUnetHTA partners) responded by returning the requested information.

Consumption of the case study medicines was seen in all countries, except for duloxetine HCl in Poland. The level of medicines use (5 years after MA) varied between the countries included in the study and across the three different medicines. The level of medicines use (5 years after MA) ranged from 13.1 – 102.0 DDDs/1000inhabitants/year for aripiprazol, from 0.0 – 401.6 DDDs/1000inhabitants/year for duloxetine HCl and from 0.66 – 465.9 DDDs/1000inhabitants/year for pregabalin.

Table 2 provides an overview of the reimbursement dates and restrictions to the use of these medicines in the various EU member states. During the study period (2004–2009), aripiprazol received a positive reimbursement decision in 17 countries. In Poland and the UK, a positive reimbursement decision was only taken after the end of the study period (Dec 2010, respectively January 2011). Duloxetine HCl and pregabalin received a negative outcome of the reimbursement decision in Poland. In the UK (England/Wales), these medicines were not assessed by the National Institute for Health and Clinical Excellence (NICE), meaning that the decision to fund these medicines is made on a local level. Because no reimbursement decision was made on a national level or the decision was made after the end of the study period, both countries were totally excluded from further analyses. Table 2 shows the variation between countries in type and ‘number’ of restrictions for reimbursement. In general, aripiprazol, duloxetine HCl and pregabalin were mostly reimbursed when used according to the indication as defined in the SPC. In 35% (aripiprazol), 41% (duloxetine HCl) and 29% (pregabalin) of the countries, additional requirements for reimbursement were applicable.

Plots of usage patterns over time of aripiprazol, duloxetine HCl and pregabalin for the various countries, identified four typical patterns: a) rapid reimbursement decision following MA with a rapid increase in use, b) ‘delayed’ reimbursement decision but rapid uptake following

Table 2 Overview reimbursement dates and restrictions per medicine and for each country

Country	Molecule								
	aripiprazol			duloxetine HCl			pregabalin		
	Reimbursement date	Restrictions	Level of restriction	Reimbursement date	Restrictions	Level of restriction	Reimbursement date	Restrictions	Level of restriction
Austria	01/06/2005	no	0	01/09/2006	SPC/p	2	01/03/2007	SPCr	2
Belgium	01/09/2005	SPC	1	01/04/2006	SPC	1	01/02/2006	SPC/b/c	3
Czech Republic	01/07/2005	SPC/p	2	01/07/2005	i/p	2	01/07/2005	SPCr/p/i	4
Denmark	05/07/2004	no	0	14/02/2005	no/a	0	08/11/2004	i	1
Estonia	01/04/2006	SPC/b	2	01/01/2006	SPCr/p/b	4	01/07/2006	No	0
Finland	01/11/2004	SPC	1	01/04/2005	SPC	1	01/12/2004	SPC	1
France	20/04/2005	SPC	1	12/12/2007	SPC	1	01/06/2006	SPC	1
Hungary	01/01/2005	SPC/a/c	3	01/01/2006	SPC/b	2	01/04/2006	i	1
Italy	01-02-2005	SPC(c)	2	01-12-2005	SPC	1	01-07-2005	SPC	1
Latvia	01/04/2006	SPC/p/b/d	4	01/07/2006	SPC/p	2	01/01/2007	i/p	2
Luxembourg	01/05/2005	SPC	1	01/05/2005	SPC	1	01/04/2005	SPC	1
Netherlands	25/10/2004	SPC	1	16/08/2005	SPC	1	21/02/2005	SPC	1
Poland	(30/12/2010)	SPC	1	Not reimbursed*	na	na	Not reimbursed	na	na
Portugal	01/10/2007	SPC/d	2	01/12/2006	SPCr	2	01/10/2005	SPC	1
Slovakia	01/07/2006	SPC	1	2005	SPC/b	2	2005	i	1
Slovenia	13/12/2004	SPC	1	12/12/2005	SPC	1	12/12/2005	i	1
Spain	17/12/2004	SPC	1	21/12/2005	SPC	1	20/01/2005	SPC	1
Sweden	09/06/2004	SPC	1	10/11/2004	SPC	1	01/02/2005	SPCr	2
UK	(2011-01-01)	SPCr	2	na**	na	na	na**	na	na

Abbreviations:

SPC = reimbursed for indications as mentioned in SPC, p = restricted to prescriber, i = restricted to indication other than in SPC, SPCr: reimbursed with restrictions (unspecified), a) conditional reimbursement as of October 2005, b) reimbursed only if other treatment is ineffective, c) reimbursed only if doctor properly documents the need, d) For some SPC indication partly reimbursed, na = not applicable

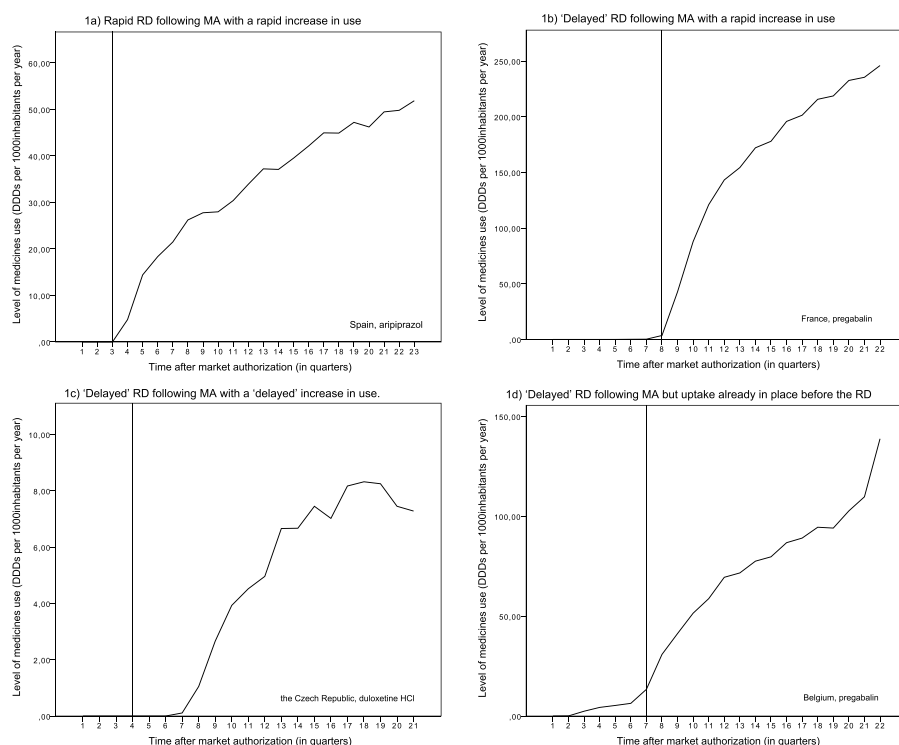
\* No sales of duloxetine HCl were seen during the study period

\*\*It has not gone through NICE technology appraisal process, therefore decision to fund is made at a local level

reimbursement decision, c) 'delayed' reimbursement decision with an even more delayed uptake, and d) 'delayed' reimbursement decision but uptake already in place before the reimbursement decision. Illustrations of these typical usage patterns (including the moment of reimbursement) are presented in Figure 1.

Table 3a illustrates the variation between countries in differences between time to reimbursement decision and time to first usage (in months). Variation between and within countries is seen in both the time to reimbursement decision date as to first usage date. Some countries, like Finland and Sweden, clearly had a similar pattern for all molecules. Usage of the case study medicines quickly followed market authorization, while the decision for reimbursement followed later, but still relatively quickly. In Latvia for example, usage of pregabalin was already in place long before a reimbursement decision was made. However, when looking at aripiprazol and duloxetine HCl, the situation is reverse in this country.

Table 3b presents the aggregated median times, calculated for each molecule. Pregabalin is standing out as it clearly shows a shorter time to first usage than to the reimbursement decision, indicating that usage is already in place before a reimbursement decision is made (as reflected by figure 1d, which was most commonly seen in the case of pregabalin). For aripiprazol and duloxetine HCl, the usage patterns most frequently identified were those as reflected by figures 1a and 1b.



**Figure 1a-d** Typical illustrations of usage patterns. Vertical line indicates the moment of reimbursement decision



**Table 3a** Time (in months) between the reimbursement decision date (RD) and the first usage date (FU) per country and molecule. Between brackets, the first number refers to the time (in months) from market authorization to reimbursement decision and the second number refers to the time from market authorization to the first usage date (in months)

	<b>aripiprazol</b> <b>Δ (MA to RD – MA to FU)</b>	<b>duloxetine HCl</b> <b>Δ (MA to RD – MA to FU)</b>	<b>pregabalin</b> <b>Δ (MA to RD – MA to FU)</b>
Austria	2.9 (11.9 – 9.0)	17.5 (20.5 – 3.0)	28.8 (31.8 – 3.0)
Belgium	-0.1 (14.9 – 15.0)	0.4 (15.4 – 15.0)	15.9 (18.9 – 3.0)
Czech Republic	3.9 (12.9 – 9.0)	-14.6 (6.4 – 21.0)	2.8 (11.8 – 9.0)
Denmark	-2.0 (1.0 – 3.0)	1.9 (1.9 – 0.0)	1.1 (4.1 – 3.0)
Estonia	-14.1 (21.9 – 36.0)	0.5 (12.5 – 12.0)	2.8 (23.8 – 21.0)
Finland	4.9 (4.9 – 0.0)	9.5 (9.5 – 0.0)	4.7 (4.7 – 0.0)
France	4.5 (10.5 – 6.0)	-6.2 (35.8 – 42.0)	10.8 (22.8 – 12.0)
Hungary	-2.1 (6.9 – 9.0)	-5.5 (12.5 – 18.0)	11.8 (20.8 – 9.0)
Italy	-1.1 (8.0 – 9.0)	5.5 (11.5 – 6.0)	-0.2 (11.8 – 12.0)
Latvia	-2.1 (21.9 – 24.0)	-5.6 (18.4 – 24.0)	23.9 (29.9 – 6.0)
Luxembourg	-1.1 (10.8 – 12.0)	4.5 (13.5 – 9.0)	5.8 (8.8 – 3.0)
Netherlands	1.7 (4.7 – 3.0)	-7.1 (8.0 – 15.0)	4.6 (7.6 – 3.0)
Portugal	12.9 (39.9 – 27.0)	-3.5 (23.5 – 27.0)	2.9 (14.9 – 12.0)
Slovakia	9.9 (24.9 – 15.0)	36.5 (48.5 – 12.0)	-3.1 (5.9 – 9.0)
Slovenia	-2.7 (6.3 – 9.0)	-3.7 (11.3 – 15.0)	5.2 (17.2 – 12.0)
Spain	-2.6 (6.4 – 9.0)	-5.9 (12.1 – 18.0)	0.5 (6.51 – 6.0)
Sweden	0.2 (0.2 – 0.0)	3.6 (3.6 – 0.0)	6.9 (6.9 – 0.0)

**Table 3b** Median time to reimbursement decision and median time to first usage per molecule

	<b>N</b>	<b>Median time from MA to reimbursement in months (25 and 75% centiles)</b>	<b>Median time from MA to first usage in months (25 and 75% centiles)</b>	<b>Median of time period between reimbursement decision date and first usage date</b>
aripiprazol	17	10.5 (6.3-14.9)	9 (6.0-15.0)	-0.09
duloxetine HCl	17	12.5 (9.5-18.4)	15 (6.0-18.0)	0.44
pregabalin	17	11.8 (6.9-20.8)	6 (3-12)	4.86

In figure 2, the level of medicines use (5 years after MA) is set out against the time to reimbursement decision. Duloxetine HCl (figure 2b) shows the largest variation in time to reimbursement decision making, whereas pregabalin (figure 2c) shows the largest variation in the level of medicines use (5 years after MA) possibly partly as a result of the time to reimbursement decision ( $R^2 = 0.31$ ).

The differences and similarities between countries across the three different medicines as shown in figure 2, are also noteworthy. Some countries showed a short time to decision making and a relatively high level of use (5 years after MA) for all three molecules (for example Denmark and Sweden). However the time to reimbursement decision can also vary for one country. Slovakia for example had a rather short time to reimbursement decision for pregabalin, an 'average' time for aripiprazol but a notable long time to a decision for duloxetine HCl. The same can be said for Luxembourg and Portugal for example. Except for pregabalin, the calculated r-squares suggest a weak relation between the level of medicines use (5 years after MA) and the time to reimbursement decision.

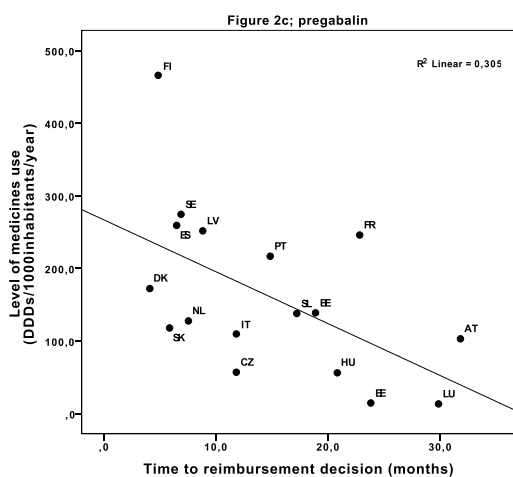
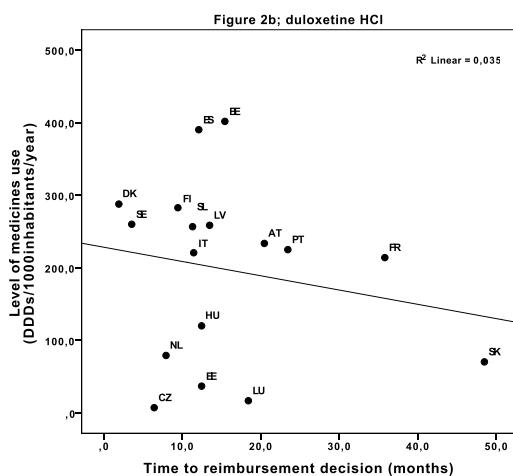
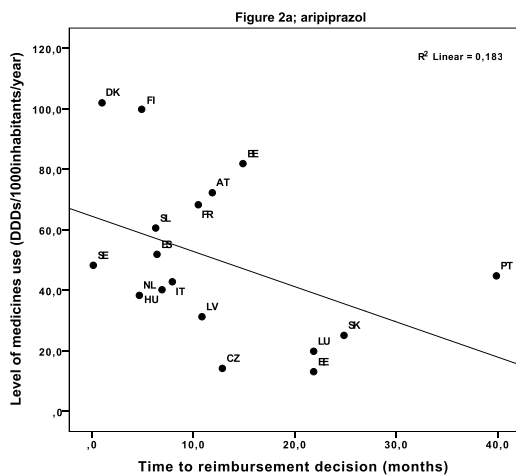
Figure 3 reflects the differences in level of use (5 years after MA) between the (grouped) number of restrictions. Mann-Whitney's U test show that for aripiprazol and duloxetine HCl the two groups differed significantly with less use in countries with more restrictions on reimbursement (p-values <0.02 and 0.01 respectively). This was not the case for pregabalin (p-value <0.38). Scatterplots and calculated r squares (0.16 for aripiprazol, 0.06 for duloxetine HCl and 0.01 for pregabalin) revealed no relation between the number of restrictions and the time to reimbursement decision.

## DISCUSSION

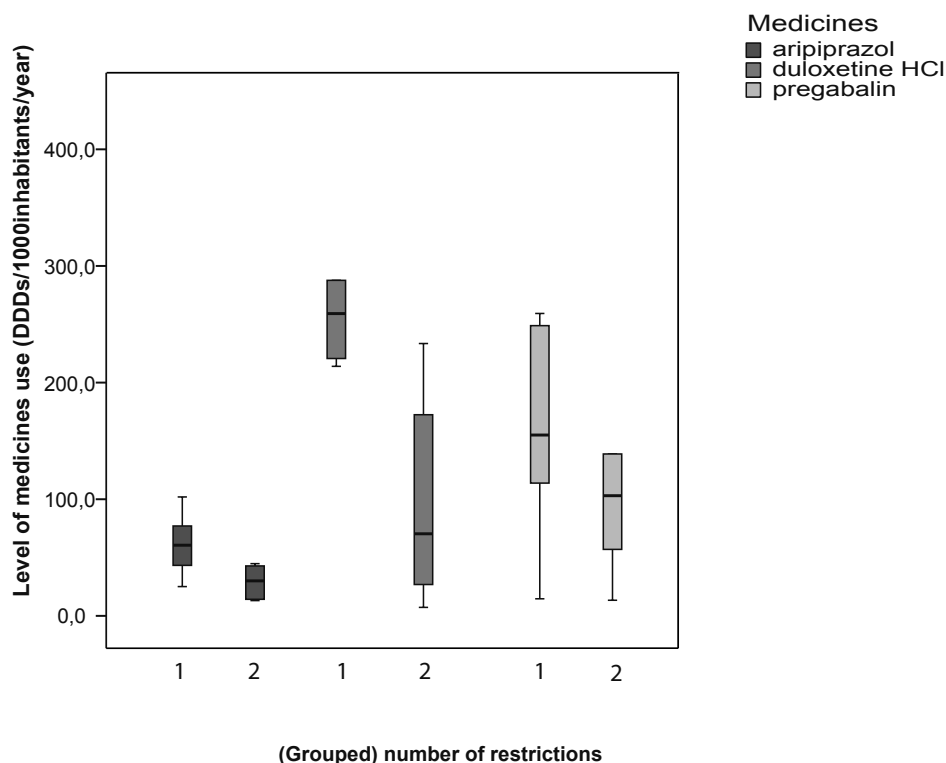
This study focused on cross-national variations in reimbursement decision making around new medicines and the effect on the availability and utilisation of those medicines. As case study medicines, three new psychotropic medicines were selected that were granted a European market authorization in 2004, are commonly used, considered as clinically relevant for some patients but generally not as major breakthroughs within their therapeutic areas. Variation in use of these medicines between patients and prescribers, and on a higher level between regions and countries, is likely to occur, due to differences in opinions and perspectives of the prescribing physician. This study indeed showed cross-national variation in the level of use of these medicines (5 years after MA), for example an almost 8 fold increase for aripiprazol was seen.

The findings of this study however, add another dimension in explaining cross-national variation in use of new medicines. The results of this study show that a) the reimbursement decision is an important element for the uptake of medicines and b) these medicines have been susceptible to variation in decision making. Furthermore, the most important finding of this study is the weak to moderate relation between the time to reimbursement decision and the level of medicines use, even 5 years after market authorization.

There is currently a debate within the European Union about the need of faster access to medicines [20,21]. This should be achieved through streamlining and reducing the duration of



Figures 2a-c Time to reimbursement decision and level of use, 5 years after market authorization



**Figure 3** Level of medicines use (5 years after MA) and (grouped) number of restrictions regarding the reimbursement per medicine. Group 1 indicates number of restrictions  $\leq 1$ , group 2 indicates that number of restrictions  $\geq 2$

national decisions on pricing and reimbursement of medicines. Our data indeed prove that uptake generally starts once the reimbursement decision is made. However, in addition our data show that streamlining and reducing the duration of national decisions on reimbursement of medicines may even have a long term effect on the level of use of new medicines.

Aggregated data for pregabalin showed that usage was in general already in place before a reimbursement decision was made. Reasons for this phenomenon are not known. It might be caused by differences in out of pocket payment. This is for example more likely in the eastern European countries with strict budgets. The medicine could also be sponsored by pharmaceuticals company, however this is often more likely with medicines for rare or lethal diseases (e.g. orphan or cancer medicines). Finally, as pregabalin was the first medicine in the EU to be officially approved for neuropathic pain, a certain clinical need may have existed causing a relatively quicker prescribing of this medicines by physicians..

To our knowledge, no data on (so many) EU member states have been previously published that combine the moment of reimbursement decision with actual usage data. The differences and similarities between countries in the moment of reimbursement

decision across the three different medicines are noteworthy. Although the reasons for these variations within a country are unknown, which is a limitation of our study, there are various possible explanations. Differences in the moment of sending along an application by the manufacturer, to have a product listed for reimbursement, can contribute to a 'delayed' reimbursement decision. In addition, it can depend on the resources available for doing the specific reimbursement assessment or a delay during the assessment because of additional data requirements (additional data have to be provided by the manufacturer). However, no relation was found between the time to reimbursement decision and the (grouped) number of restrictions implicating that a longer time to decision making does not necessarily mean that the assessment is complicated and more time is needed to think over suitable restrictions. The OECD Pharmaceutical Pricing Policies in a global market report showed great variation in Europe in the average number of days from reimbursement application to decision [21]. Some countries showed no delay as medicines are reimbursed as soon as they are approved, unless or until they are added to the negative list. This is for example reflected by the usage data from the UK, where uptake is seen directly after granting of the market authorization. However, the UK public healthcare system is relatively complex, with a range of different trusts and authorities deciding on healthcare provision. The Primary Care Trusts (PCTs) are responsible for delivering health care and health improvements within a local area. They have their own budgets and set their own priorities, within the overriding priorities and budgets set by the relevant Strategic Health Authority and ultimately the national Department of Health [22]. UK evaluations by NICE feed regional reimbursement decisions. In contrast to the methods of healthcare evaluation in other countries, NICE does not evaluate all interventions as they reach the market, neither does it evaluate all (new) medicines. This is seen in the case of aripiprazol where NICE made a decision in January 2011 while the medicine was already on the market and directly used.

Restrictions to reimbursement seemed also to have a slight effect on the level of use. Our results showed that this was the case for aripiprazol and duloxetine HCl. The level of use (5 years after MA) was significant higher in countries with less than two restrictions for reimbursement. However, further study is needed to elaborate more on this issue and to identify which restrictions are most stringent. The time taken to a reimbursement decision did not seem to have an effect on the number of restrictions.

In many countries the medicines reimbursement system is rather inflexible: reimbursement is either granted or not. Uncertainties in reimbursement decision making, due to the clinical evidence and/or the expectations of the new medicine, may result in delays and false positive or false negative decisions. The consequences of these uncertainties may cause 1) delay of decision making, 2) a negative reimbursement decision while at a later stage it will become clear that the treatment does have an added value (false negative decision); and 3) a positive reimbursement decision while at a later stage it will become clear that the treatment does not have an added value (false positive decision). In the first case, availability of a new treatment to patients is unnecessarily late. In the second case, patients are denied access to effective treatments. In the third case, the available budget had better been spent on other, effective treatments [23]. A solution for these consequences might be to apply conditional reimbursement to those

medicines for which their clinical relevance still has to be definitely proofed. The data provided by EUnetHTA partners identified some of the above mentioned conflicts. In Denmark for example, duloxetine HCl was first made eligible for general reimbursement. Eight months later it was made eligible for conditional reimbursement for a certain indication.

In conclusion, this study presented the influence of cross-national variation in policy decision making around the reimbursement of new medicines on the uptake and level of use of three relatively new psychotropic medicines. The results show that these medicines are susceptible to variation in policy decision making. Decision makers should realize the impact of the (speed of) reimbursement decision on the uptake and level of use as delays in reimbursement decisions may have an impact on access to and use of new medicines even after 5 years following market authorization. When explaining causes of cross-national variation in medicines use, the effects of the (speed of) reimbursement decision should be taken into account.

## ACKNOWLEDGEMENTS

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# CHAPTER 3.5

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## **FUTURE OF THE EUROPEAN UNION REGULATORY NETWORK IN THE CONTEXT OF THE UPTAKE OF NEW MEDICINES**

Joëlle Hoebert, Alar Irs, Aukje Mantel-Teeuwisse, Hubert Leufkens

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With the European economy in the midst of the deepest recession since the 1930s and countries struggling to weigh up national and community interests, one may overlook accomplishments made in other areas of the European co-operation. Since the start of the European Union (EU) medicines approval system in 1995, the European regulatory environment has faced many challenges, but also made ample progress. Significant achievements are seen in unifying and improving regulatory practices, streamlining the way of bringing medicinal products to the clinic, thereby improving how new medicines become available to patients in the EU in a harmonized and evidence-based way [1,2]. With the European Medicines Agency (EMA) co-ordinating a wide array of regulatory procedures, EU member states are contributing in many ways to the regulatory network, e.g. as rapporteur of individual dossiers, by work sharing, guideline development and cross learning. Recently, both the EMA and the Heads of Medicines Agencies (HMA) published their future strategy papers (i.e. European Medicines Agency Road Map to 2015: The Agency's contribution to Science, Medicines, Health and the HMA; A Strategy for the Heads of Medicines Agencies 2011–2015), aiming at strengthening the European regulatory network and its contribution to patients' access to medicinal products, public health and innovation [3,4].

While the crucial role of the EMA as the engine of the European pharmaceutical regulatory system is evident, the roles of national competent authorities remain equally important. Apart from the EMA, the EU regulatory network consists of around 31 national competent authorities who are responsible for an array of regulatory tasks related to human medicinal products in their national systems [5]. They also provide scientific footing of the system via the membership of the EMA scientific committees, such as the EMA Committee for Medicinal Products for Human Use (CHMP). The CHMP is mainly composed of the members nominated by the 27 EU member states and the EEA-EFTA states Iceland and Norway, who heavily rely on support from their national agencies with respect to the reviewing and assessment of the claims in the dossiers submitted by industry and the benefit-risk assessment related to a product application [6]. The system of rapporteurs is seen as the backbone of the EU Centralized Procedure, but there are concerns about the large variation among EU member states regarding their individual contributions in terms of the number of (co-)rapporteur roles. Both previously mentioned strategy reports underpin the importance of a re-balance between member states in work-sharing and showing leadership in Centralized Procedures.

### **Variability in uptake of new medicines and regulatory roles across European member states**

We evaluated variation in rapporteur contributions to the EU regulatory network between EU member states in light of the level of availability and market uptake of new medicines in the same EU countries. Previous research has proposed various explanations for this variation ranging from lack of resources and expertise to intentional national policies [7, 8]. We approached this issue from another angle and present data on how new medicinal products approved in 2004 (Table 1) were adopted by national clinical practices as measured through IMS data. IMS collects pharmaceutical consumption data from a mixed sample of wholesalers, hospitals and/or dispensing outlets such as pharmacies and drug stores [9]. In this analysis,

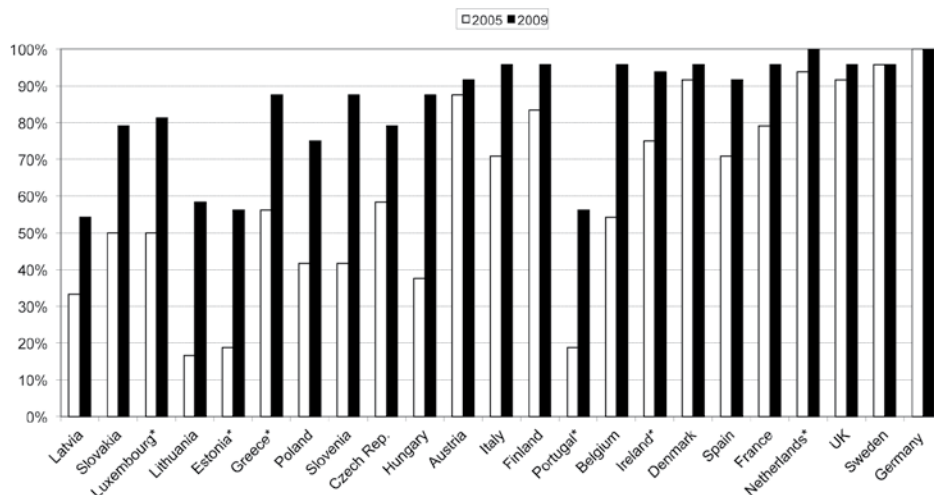
**Table 1** Centrally approved medicines in the EU in 2004 (n=24)\*

International Nonproprietary Name	Brand name	Indication	WHO ATC code	Most important usage setting
abacavir / lamivudine	Kivexa®	HIV Infections	J05AR02	Outpatient
anagrelide	Xagrid®	Essential Thrombocythemia	L01XX35	Outpatient
aripiprazole	Abilify®	Schizophrenia/Bipolar Disorder	N05AX12	Outpatient
atazanavir	Reyataz®	HIV Infections	J05AE08	Outpatient
bivalirudin	Angiox®	Angioplasty, Acute Coronary Syndrome	B01AE06	Inpatient
bortezomib	Velcade®	Multiple Myeloma	L01XX32	Inpatient
cetuximab	Erbix®	Head and Neck, and Colorectal Neoplasms	L01XC06	Inpatient
cinacalcet	Mimpara®	Hyperparathyroidism, Parathyroid Neoplasms	H05BX01	Outpatient
cladribine	Litak®	Leukemia, Hairy Cell	L01BB04	Inpatient
darifenacin hydrobromide	Emselex®	Urinary Incontinence	G04BD10	Outpatient
duloxetine hydrochloride	Cymbalta®, Xeristar®	Diabetic Neuropathies, Depressive Disorder	N06AX21	Outpatient
fibrinogen/thrombin	TachoSil®	Surgical Hemostasis	B02BC30	Inpatient
fosamprenavir calcium	Telzir®	HIV Infections	J05AE07	Outpatient
fulvestrant	Faslodex®	Breast Neoplasms	L02BA03	Outpatient
ibandronic acid	Bondenza® / Bonviva®	Postmenopausal osteoporosis	M05BA06	Outpatient
ibritumomab tiuxetan	Zevalin®	Follicular Lymphoma	V10XX02	Inpatient
insulin detemir	Levemir®	Diabetes Mellitus	A10AE05	Outpatient
insulin glulisine	Apidra®	Diabetes Mellitus	A10AB06	Outpatient
mitotane	Lysodren®	Adrenal Cortex Neoplasms	L01XX23	Outpatient
octocog alfa	Advate®	Hemophilia A	B02BD02	Inpatient
oxybutynin	Kentera®	Urge Urinary Incontinence	G04BD04	Outpatient
pemetrexed	Alimta®	Non-Small-Cell Lung Carcinoma	L01BA04	Inpatient
pregabalin	Lyrica®	Anxiety Disorders, Epilepsy, Neuralgia	N03AX16	Outpatient
strontium ranelate	Dukoral®	Osteoporosis, Postmenopausal	M05BX03	Outpatient

\*A total of 29 medicines obtained approval through the Centralised Procedure. Medicines were excluded if approval in 2004 concerned extension of the indication or a new orphan designation (n=2), if the medicine had been on the European market for many years and the current utilisation of the medicines had been influenced by many other factors (n=1) or because their usage was so low that they could not be divided into quartiles (n=2)

the uptake of all new medicines centrally approved in 2004 was followed in the subsequent 5 years (2004–2009). Uptake of each new medicine with a European license granted in 2004 was measured by volume (i.e. standardized units) and expressed per 1000 inhabitants per year. Population statistics were obtained from the website of the United Nations, Department of Economic and Social Affairs for the years 2006 and 2009 [10].

In Figure 1, the actual availability in 2005 and 2009 of these medicines is shown for each individual EU member state. This figure demonstrates the variation in actual availability of these medicines



**Figure 1** Availability (in %) of all centrally approved medicines (2004) in 2005 and 2009. Countries are ordered (increasing order) on the x-axis according to their number of rapporteur roles between 2004 and 2009. Data used for this study were obtained for all 25 EU member states (per 01/05/2004), except for the Mediterranean islands of Malta and Cyprus for which IMS had no data. Within countries, IMS uses the same method but the methodology used varies between countries and depends on the nature of the pharmaceutical supply systems. IMS collects data in over a hundred countries world-wide. Volume data was expressed in standard units (SU). This is a measure used by IMS derived from the number of doses. It is measured differently depending on the formulation of the medicine. Usually one SU equals one capsule, one tablet, one prefilled syringe, one dose of inhaled medicine or 5 ml of an oral suspension etc. If IMS does not collect data from all suppliers in a country they project the sample of a particular distribution channel to the national level. A medicine was defined as available if consumption in that year was  $\geq 100$  SU. The years 2005 and 2009 were chosen to see the differences between fast and slow uptakers. Countries are ordered along the X- axis according to their contribution to the EU regulatory system with countries on the left hand side contributing to a lesser extent than countries on the right hand side. \* For certain countries only retail data, and no hospital data were available from IMS. These are marked with an asterisk. In these countries availability was determined for medicines used in the outpatient setting only (see table 1)

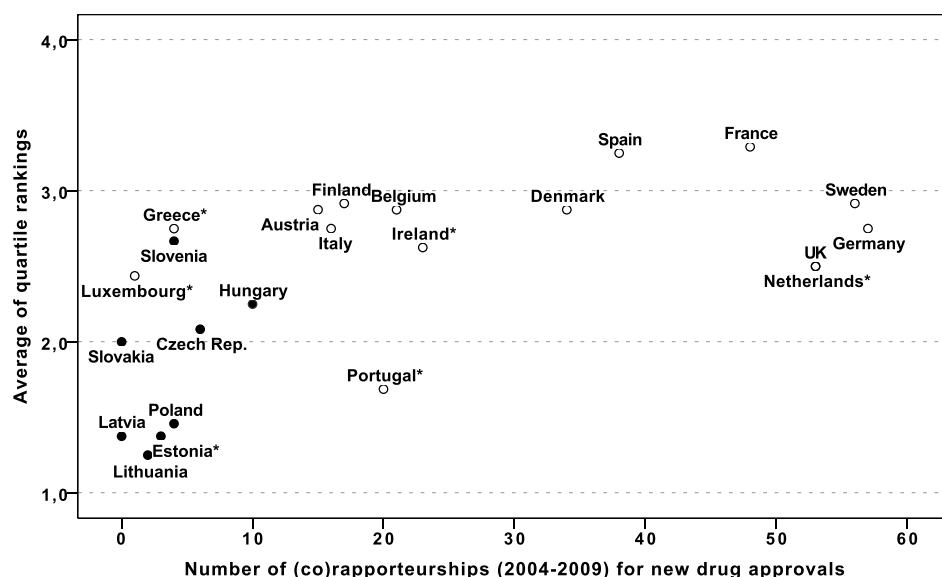
between the individual EU countries, a strong factor behind variation in the uptake of these new medicines. In some countries like Portugal and the Baltic States over 40% of the studied products were not available at all, even 5 years after the moment of a formal EU market authorization.

As a next step, for each product the volumes consumed in 2009 across all countries were divided into four equal parts (quartiles). Each EU member state was ranked according to their consumption into a quartile. A member state was ranked in quartile one when the market uptake of the new medicine was within the lowest 25% of the data, member states were ranked in quartile two when the market uptake of the new medicine was above the cut off lowest 25% of data, but beneath the median (second quartile), in quartile three if market uptake of the new medicine was above the median but below the cut off highest 25% of data and in quartile four when the market uptake of the new medicine was above this point. Finally, the average ranking of quartiles per EU member state for all medicinal products was calculated and crossed against the number taking the lead in a Centralized Procedure as a (co-)rapporteur between 2004 and 2009 (Figure 2).

Figure 2 shows the wide variability between EU member states in contributions to the Centralized Procedure as rapporteur vs. the level of uptake of new medicines. Countries in the upper right quadrant ( $n = 4$ ) show a high uptake of medicines and frequent contributions as rapporteur for products following the Centralized Procedure. The contribution as rapporteur of Denmark, Spain and France is below those member states that contribute most, but they show the highest uptake of new medicines in Europe. In the upper left quadrant extending almost to the middle, there are countries in which the uptake of new medicines appears quite high despite a low or moderate contribution as rapporteur. The lower left quadrant includes countries, predominately newer EU member states, with a relatively low uptake of new medicines and small numbers of contributions as rapporteur compared with other EU member states. Finally, Portugal is a significant outlier with a contribution that can be ranked as moderate but with a limited uptake of new medicines; most likely due to the limited availability of medicines (see Figure 1). A similar result was found when analyzing data for 2006 instead of 2009, when assessing medicines used in the in- or out-patient setting only, but also when limiting to or excluding the expensive (oncology) medicines.

### Understanding such variability between EU member states and its implications

This study shows that innovative medicines are not equally available for all citizens in the EU in a timely and equitable manner. The discrepancy in the uptake of medicines between EU member



**Figure 2** Average uptake of all centrally approved medicines in 2004 and the number of rapporteur roles in 2004-2009 of each member state. \*For certain countries only retail data, and no hospital data were available from IMS. These are marked with an asterisk. Filled in markers ( $n=8$ ) refer to countries that joined the European Union per 1 May 2004, the open markers ( $n=15$ ) refer to older EU member states

states seems to reflect to a certain degree the economic situation and resource possibilities of these countries. Our analysis confirms a correlation between the market uptake of new medicines and key macroeconomic variables such as gross domestic product and government expenditures, as also demonstrated by others studies [11–13]. Although barriers to market authorization of medicinal products have virtually diminished across Europe, regulatory practices affecting actual prescribing and usage (i.e. reimbursement and pricing, formulary policies, promotion regulation) show large variation, significantly influencing the availability and uptake of new medicines into clinical practice. This is also an area where the pharmaceutical industry which benefits significantly from a centralized and harmonized regulatory system, but who is not always willing to market an approved EU product in a low-resourced market, should show more and sustained responsibility.

As stated by the EMA itself, a critical factor for the Agency's success has been the provision of high quality scientific resources for the evaluation and supervision of medicinal products by individual EU member states. Pivotal for achieving this is the strengthening of the co-operation of all individual member states. Our analysis stresses that the required input of high quality specialist expertise provided by the member states to the EU regulatory system is not proportionally shared. There may be many factors contributing to this variability, ranging from constraints of resources, limited (scientific) expertise and/or experience at the national competent authorities that is needed to be appointed as rapporteur or the lack of interest in contributing to the assessment of medicinal products that at the end of the day are not used anyhow by the citizens of the concerned individual member state. The variability in rapporteurships does not seem to relate to the size of the country or the size of the national competent authority. Sweden or the Netherlands do not appear as extremely big countries or national competent authorities but contribute in a sustained fashion. Another explanation could be that it is more difficult to participate actively in the CHMP for newer EU member states as the older EU member states are more settled, resulting in more rapporteurships based on previous experiences or involvement during the clinical development phase (e.g. scientific advice) or because they have the best available expertise in the EU on the relevant scientific area (as requested in the 'CHMP rules of procedure') [14]. In terms of solutions it is important to build further in the European regulatory network on sustainable resources, expertise and regulatory science, but also the political will of member states to invest in contributing to the assessment of new products remains a critical factor.

It should be kept in mind, however, that this analysis only includes the contribution of EU member states to the centralized system in terms of (co-)rapporteurships. There are various other possibilities for countries to be actively involved in the EU regulatory system, such as acting as reference member states in the Mutual Recognition Procedures or the Decentralized Procedures or being involved in paediatric deferrals. Contributions to these EU procedures might be, for some countries like Estonia or Slovakia, more interesting as much of these procedures relate to generic products with high consumption rates in these countries. Statistics of the HMA and EMA show a prominent role of these countries in these EU procedures. Estonia, for example, is often involved in the evaluation of the paediatric investigation plans.

Furthermore, it should be noted that the peer review process and work sharing projects also contribute to the learning process, a process that is even more established through the twinning programme of the EMA [15]. New Member States will achieve a progressive gain of experience and confidence and will be keen on being more involved. Even if Member States do not directly take (co)-rapporteurship their contribution to the discussions is considered as important and useful [16]. Every sustainable system of collaboration between countries depends heavily on a certain level of proportionality, whether it is economics or the regulation of medicinal products. Bringing new medicinal products to the European market in terms of licensing has been harmonized over the last decades in a significant way. However, actual availability and uptake of these products in EU member states still varies strongly. This is not a new finding and is inherent to the fact that EU member states remain responsible for the way they build and fund their national health care systems [7,8,13]. However, when variability in contributions to the pharmaceutical regulatory system goes hand in hand with variability of actual prescribing and usage, as reflected by the countries (the predominantly newer EU member states) located in the lower left quadrant of Figure 2, there is ample reason for concern about sustainability of the regulatory network that depends heavily on European partnership and community responsibility. Such responsibility is likely to blossom better in an environment where work sharing in bringing new pharmaceutical products to the market pays off in also safeguarding patients' interest on a national level. Obviously, this is not the case.

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# CHAPTER 4

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MONITORING OF A SPECIFIC POLICY  
IN THE NETHERLANDS



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# CHAPTER 4.1

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## REIMBURSEMENT RESTRICTION AND MODERATE DECREASE IN BENZODIAZEPINE USE IN GENERAL PRACTICE

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## ABSTRACT

### Purpose

To limit misuse and save costs, on January 1, 2009, benzodiazepines were excluded from the Dutch reimbursement list when used as anxiolytic, hypnotic, or sedative. This study aims to assess the impact of this reimbursement restriction on benzodiazepine use in patients with newly diagnosed anxiety or sleeping disorder in general practice.

### Methods

Was conducted a retrospective observational database study deriving data on diagnoses and prescriptions from the electronic health records–based Netherlands Information Network of General Practice (LINH). We looked for patients aged 18 years and older with an incident diagnosis of sleeping disturbance (International Classification of Primary Care code: P06) or anxiety (P74, P01) between January 2008 and December 2009. Incidence of these diagnoses, benzodiazepine use, and initiation of selective serotonin reuptake inhibitor (SSRI) treatment was compared between 2008 and 2009.

### Results

In total, we identified 13,596 patients with an incident diagnosis of anxiety (3,769 in 2008 and 3,710 in 2009) or sleeping disorder (3,254 in 2008 and 2,863 in 2009). The proportion of patients being prescribed a benzodiazepine after a diagnosis was lower in 2009 than in 2008 for both anxiety (30.1% vs 33.7%  $P<.05$ ) and sleeping disorder (59.1% vs 67.0%,  $P<.05$ ), as was the proportion of patients with more than 1 benzodiazepine prescription for both anxiety (36.4% vs 42.6%,  $P<.05$ ) and sleeping disorder (35.0% vs 42.6%,  $P<.05$ ). We found no increase in the use of alternative treatment for anxiety with SSRIs.

### Conclusions

The reimbursement restriction has led to a moderate decrease in the number of incident diagnoses and initiation of benzodiazepine use in patients with newly diagnosed anxiety or sleeping disorder. This finding indicates that in settings where no such reimbursement opportunities exist, physicians have room to reduce benzodiazepine prescribing.

## INTRODUCTION

Benzodiazepines are widely used in the treatment of anxiety, panic disorders, and insomnia, as well as of neurologic and rheumatologic conditions [1-3]. Long-term use of benzodiazepines is associated with an increased risk of abuse, misuse, and adverse events [4-6]. Expert bodies, such as the Netherlands College of General Practitioners, have long advised that use of benzodiazepines should be limited to short courses for acutely distressed patients and generally be avoided in elderly people [7]. Nevertheless, about 30% of the patients using benzodiazepines are chronic users, predominantly for insomnia [2,8].

In the Netherlands, after consultation with patient and professional organizations, a change was made in the reimbursement status of benzodiazepines that was announced mid 2008 and came into force on January 1, 2009. From that date on, benzodiazepines were excluded from the Dutch reimbursement list (full reimbursement regardless of diagnosis or other restrictions) when used as anxiolytic, hypnotic, or sedative [9,10]. Coverage remained for a limited number of indications, such as epilepsy, palliative sedation, or multiple psychiatric disorders, if no alternative treatment was available [11]. The rationale for this restriction was to reduce the use of these medicines to a few specific patient subpopulations, to avoid irregular (chronic) use of benzodiazepines, and to limit the health care costs. Although costs per prescription are €12 to €16, macro-level costs were high because of the volume of benzodiazepine use.

Several studies have shown the importance of studying the effects of restrictions on reimbursement for pharmaceuticals [12-14]. Policy measures may not always be successful if patients shift to other (costly) treatments or measures do not necessarily lead to clinical benefits, as shown by Wagner et al. [15]. The Dutch Foundation for Pharmaceutical Statistics showed a 16% reduction in overall use of benzodiazepines and 14.5% fewer chronic users in 2009 compared with previous years [16]. Nevertheless, it is unknown whether this decline was the result of a decrease in initiating or an increase in discontinuation of benzodiazepines or a decrease in the number of patients given a diagnosis for which a benzodiazepine may be prescribed. To our knowledge, no studies have assessed the impact of the reimbursement restriction on specific diagnoses and initiation of benzodiazepines. Previous studies concluded that it is particularly important to limit the number of patients starting with benzodiazepines, as approximately 30% of all new patients continue use for a longer period and may display inappropriate use [17,18].

The objective of this study was to assess whether general practitioners made fewer new diagnoses of either sleeping disorder or anxiety and whether fewer benzodiazepines were prescribed for those patients once their condition was diagnosed. Furthermore, we aimed to study the possible unintended consequences of the reimbursement restriction by assessing whether patients with newly diagnosed anxiety were given prescriptions for selective serotonin reuptake inhibitors (SSRIs) instead. Finally, we assessed whether new users of benzodiazepines discontinued their medication earlier after the regulatory change in January 2009 or added or shifted more frequently to treatment with SSRIs when anxiety was diagnosed.

## METHODS

### Settings

General practice data were derived from the electronic health records–based Netherlands Information Network of General Practice (LINH), a network of general practices across the country [19,20]. LINH practices register standardized information on all health problems reported within a consultation, including information on prescribed medicines. Each patient is identified with an anonymous unique patient identification code. Patients are representative of the Dutch population with respect to age and sex. LINH observational studies, which are carried out according to Dutch legislation on privacy, are not obligated to obtain written informed consent. The LINH database includes information on patient sex, year of birth, and clinical diagnoses, which are coded using the International Classification of Primary Care (ICPC) scheme [21]. LINH general practitioners register every prescription, which is coded according to the Anatomical Therapeutic Chemical (ATC) Classification Index [22]. Only general practices with complete data during the study period were included ( $n = 95$  practices).

### Study Population and Measures

All patients aged 18 years and older with incident diagnoses of sleep disturbance (ICPC code P06) and anxiety disorder (ICPC codes P74, P01) in 2008 and 2009 were identified. Incident was defined as not having had this diagnosis in the 365 days before the diagnosis of interest. Patients were included only when they were continuously registered between January 2007 and December 2009 and had complete information on sex and year of birth. For each patient with an incident diagnosis, we assessed whether the patient was given a prescription for a benzodiazepine (ATC codes N05BA, N05CD, N05CF), either on the same date or within 7 days from the diagnosis date. The duration of each prescription was set at 30 days, which is the standard policy in the Netherlands. We assessed treatment persistence for patients receiving more than 1 benzodiazepine prescription. Patients were considered to have discontinued treatment when no new benzodiazepine prescription was issued in 90 days after the theoretical end date of the previous prescription (30 days). Furthermore, we assessed whether there was a change in the number of patients actually initiating SSRIs (ATC code N06AB) after an incident diagnosis of anxiety between 2008 and 2009 and whether patients were switched to a SSRI (in case of discontinuation of benzodiazepine use) or had an SSRI added to their treatment.

### Data Analysis

Incidence rates per quarter were calculated by dividing the number of patients with incident diagnoses by the population at risk to assess incident diagnoses of sleeping disorder and anxiety over time. Risk differences in corresponding quarters in 2008 and 2009 and 95% confidence intervals (CIs) were calculated. We defined population at risk as patients not having or having had a diagnosis of anxiety or sleeping disorder in the 365 days before inclusion. Rates were stratified by sex and age-group (18 to 44 years, 45 to 65 years, 66 to 75 years, and older than 75 years). Differences in proportion of patients who started with a benzodiazepine prescription and proportion of patients with 1 benzodiazepine prescription between 2008 and 2009 were calculated using the Pearson  $\chi^2$  test.



Kaplan-Meier survival curves were constructed for patients with more than one benzodiazepine prescription, to visualize the difference in time to discontinuation between patients starting with benzodiazepine use in 2008 (before policy change) and those starting with benzodiazepine use in 2009 (after policy change). Because discontinuation could be evaluated only if at least 120 observation days were available between the date of treatment initiation and the end of the calendar year (fixed prescription duration of 30 days and a 90-day allowable gap between prescriptions), only patients who started benzodiazepine use in the first 8 months of 2008 and 2009 were included in this analysis. Cox regression analysis was applied to estimate the strength of the association between calendar year and the risk of discontinuation among patients with more than one benzodiazepine prescription, and was expressed as a hazard ratio (HR) with 95% confidence intervals. Age and sex were considered potential confounders. Because patients may be using concurrent benzodiazepine medications for indications other than anxiety or sleeping disorder, a sensitivity analysis was conducted to assess whether there was a difference between patients using benzodiazepines for sleeping disorder or anxiety only or using concurrent benzodiazepines for other indications. A sensitivity analyses was conducted to assess the influence of our definition of benzodiazepine discontinuation by expanding the 90-day period to 180 days and by defining incident as not having had this diagnosis in the 180 days before. Beforehand, multilevel analyses were conducted to test for clustering effects within general practices; because intraclass correlation coefficients were low (<1.5%), we decided not to use a multilevel approach. Analyses were performed in SPSS 16.0.2 (SPSS Inc, Chicago, Illinois) and MLwiN 2.11 (multilevel) (Centre for Multilevel Modeling, University of Bristol, Bristol, United Kingdom).

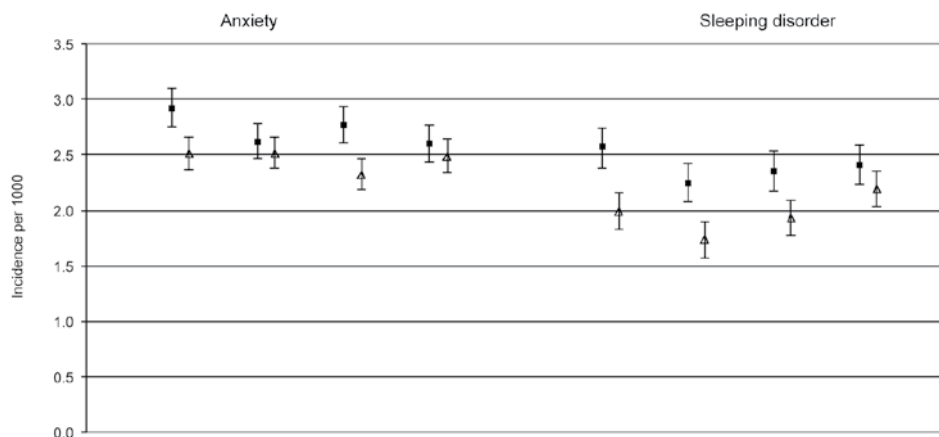
## RESULTS

In total, we identified 13,596 patients with an incident diagnosis of anxiety ( $n=7,479$ ) or sleeping disorder ( $n=6,117$ ) in the period 2008-2009. Figure 1 shows the incidence of both diagnoses for each quarter in 2008 and 2009. There was a statistically significant lower incidence of sleeping disorders in the first 3 quarters of 2009 compared with these respective quarters in 2008. For anxiety, diagnoses in the first and third quarter of 2009 were significantly lower compared with diagnoses in the first and third quarter of 2008.

Table 1 displays the characteristics of patients with incident diagnoses for anxiety and sleeping disorder in 2008 and 2009. For both disorders, the proportion of women was higher than men. The proportion of patients being prescribed a benzodiazepine following a diagnosis was slightly lower in 2009 than in 2008 for both anxiety (33.7% vs 30.1%,  $P<0.05$ ) and sleeping disorder (67.0% vs 59.1%,  $P<0.05$ ). Stratification by sex and age showed similar results. A sensitivity analysis restricted to patients with a first diagnosis in the index year with no previous diagnosis within the previous 180 days, showed similar results (data not shown). The decrease in patients being prescribed a benzodiazepine for anxiety was mostly seen in patients with *ICPC* code P01 (54.1% vs 45.9%,  $P<0.05$ ). For *ICPC* code P74, prescriptions decreased from 50.3% to 49.7% ( $P>0.05$ ).

**Table 1** Initiation of benzodiazepine treatment among patients with incident diagnoses of anxiety or sleeping disorders

	Anxiety				Sleeping disorders			
	2008		2009		2008		2009	
	N° of diagnoses	N° of benzodiazepine prescribed	N° of diagnoses	N° of benzodiazepine prescribed	N° of diagnoses	N° of benzodiazepine prescribed	N° of diagnoses	N° of benzodiazepine prescribed
Overall	3769	1270 (33.7%)	3710	1116 (30.1%)*	3254	2181 (67.0%)	2863	1691 (59.1%)*
Gender								
Men (%)	1205	410 (34.0%)	1209	359 (29.7%)*	1171	709 (60.5%)	1048	551 (52.6%)*
Women (%)	2564	860 (33.5%)	2501	757 (30.3%)*	2083	1472 (70.7%)	1815	1140 (62.8%)*
Age categories								
18 – 44 (%)	1721	419 (24.3%)	1716	378 (22.0%)	1025	639 (62.3%)	836	442 (52.9%)*
45–65 (%)	1418	566 (39.9%)	1330	471 (35.4%)*	1399	969 (69.3%)	1222	750 (61.4%)*
66 – 75 (%)	331	161 (48.6%)	358	151 (42.2%)*	419	296 (70.6%)	380	238 (62.6%)*
> 75 (%)	293	124 (42.3%)	306	116 (37.9%)*	411	277 (67.4%)	425	261 (61.3%)*

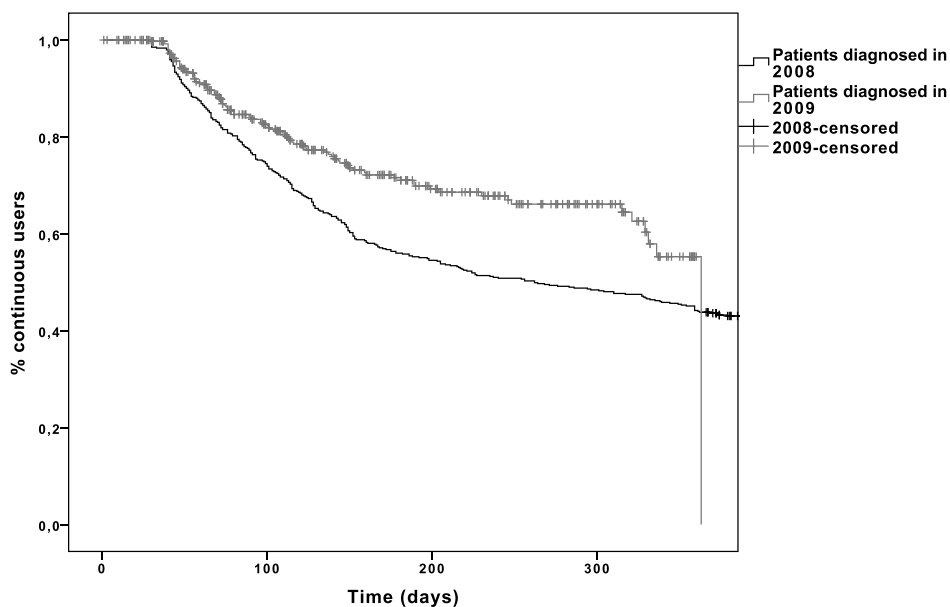


**Figure 1** Incident diagnoses for anxiety and sleeping disorder in 2008 (■) and 2009 (Δ) and their 95% confidence intervals

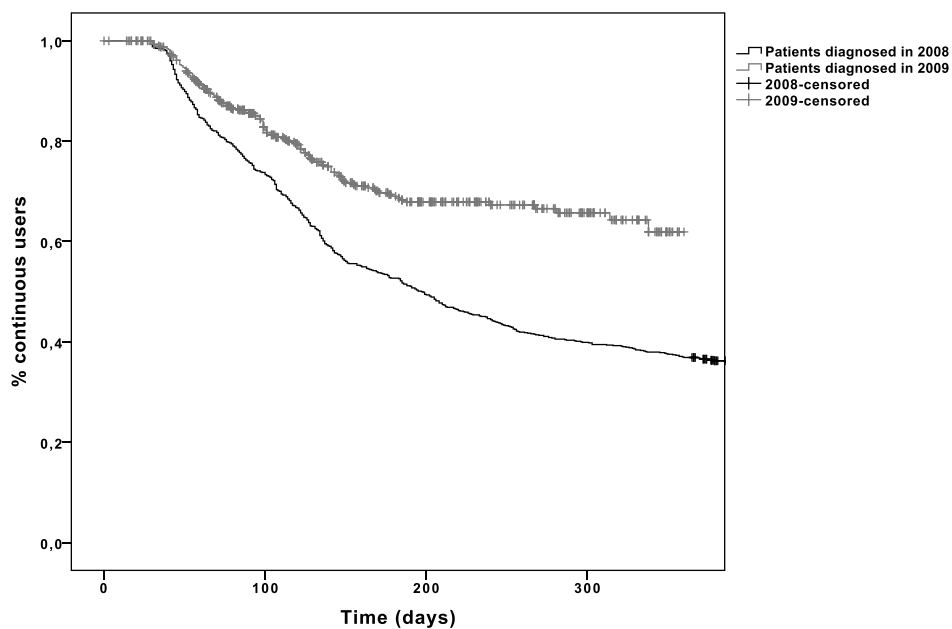
Table 2 shows that for patients with benzodiazepine prescriptions after a diagnosis, the proportion of patients being prescribed more than 1 benzodiazepine was lower in 2009 than in 2008 for both anxiety (36.4% vs 42.6%,  $P<0.05$ ) and sleeping disorders (35.0% vs 42.6%,  $P<0.05$ ).

The Kaplan-Meier curves for the years 2008 and 2009, illustrating the time to discontinuation after initiation of at least 2 benzodiazepine prescriptions, are shown in Figures 2a and 2b. Cox proportional hazards analysis was used to compare the risk of discontinuation between patients starting benzodiazepine use in 2008 and patients starting benzodiazepine use 2009. For patients with newly diagnosed anxiety, no difference in discontinuation rates was observed ( $HR=0.87$ ; 95%CI, 0.68-1.11) with newly diagnosed sleeping disorder in 2009 had a lower risk of discontinuation than did patients with newly diagnosed sleeping disorder in 2008 ( $HR=0.63$ ; 95%CI, 0.52-0.76). Similar results were seen when analyzing a subcategory; patients with benzodiazepines prescriptions for only the indication of interest (for anxiety,  $HR=0.85$ ; 95%CI, 0.64-1.13; for sleeping disorder,  $HR=0.59$ ; 95%CI, 0.47-0.75). Adjustment for age and sex had no effect on the risk estimates.

The number of patients actually starting SSRI treatment after a diagnosis of anxiety was low. In 2008 and 2009, only 232 (6.2% of patients with new diagnosis) and 196 patients (5.3%) started SSRI treatment, respectively ( $P>0.05$ ). The addition of an SSRI treatment was also infrequent: 57 (1.5%) of the patients who had anxiety newly diagnosed in 2008 added a SSRI to their current treatment of anxiety compared with 29 (0.8%) in 2009. The reimbursement restriction had no effect on switching to SSRI treatment among patients discontinuing benzodiazepine treatment when anxiety was diagnosed. Only 12 (0.3%) patients with newly diagnosed anxiety in 2008 who stopped using benzodiazepines switched to treatment with SSRIs. In 2009, only 2 patients switched (0.1%).



**Figure 2a** Kaplan Meier curves for the years 2008 and 2009, illustrating time to discontinuation after initiation of at least two benzodiazepine prescriptions in patients being newly diagnosed with anxiety



**Figure 2b** Kaplan Meier curves for the years 2008 and 2009, illustrating time to discontinuation after initiation of at least two benzodiazepine prescriptions in patients being newly diagnosed with sleeping disorder

**Table 2** Number and percentage of patients with more than one benzodiazepine prescription when newly diagnosed with anxiety or sleeping disorders

	Anxiety		Sleeping disorder	
	2008	2009	2008	2009
Overall (%)	541 (42.6%)	406 (36.4)*	930 (42.6%)	592 (35.0%)*
<b>Gender</b>				
Men (%)	181 (44.1%)	129 (35.9%)*	289 (40.8%)	195 (35.4%)
Women (%)	360 (41.9%)	277 (36.6%)*	641 (43.6%)	397 (34.8%)*
<b>Age categories</b>				
18 – 44 (%)	152 (36.3%)	113 (29.9%)	218 (34.1%)	119 (26.9%)*
45–65 (%)	236 (41.7%)	165 (35.0%)*	383 (39.5%)	235 (31.3%)*
66 – 75 (%)	71 (44.1%)	69 (45.7%)	148 (50.0%)	89 (37.4%)*
> 75 (%)	82 (66.1%)	59 (50.9%)*	181 (65.3%)	140 (53.6%)*

\*Statistically significant at  $p < 0.05$  for 2008 versus 2009

## DISCUSSION

We evaluated the impact of the reimbursement restriction on benzodiazepines use in patients with newly diagnosed anxiety or sleeping disorder and found that the incidence of sleeping disorders and anxiety was lower in the first 2 to 3 quarters after the policy change. Additionally, the probability of receiving a benzodiazepine prescription was, although modest, significantly lower in 2009 than in 2008. The decrease was most prominent in patients with newly diagnosed sleeping disorder. Among those treated with benzodiazepines, more patients received only 1 prescription in 2009. Patients with newly diagnosed sleeping disorder who received more than 1 benzodiazepine prescription discontinued their treatment earlier in 2008 than in 2009. This phenomenon was not observed in patients with newly diagnosed anxiety. No shifts to treatment with SSRIs have been observed.

We found that the number of consultations for incident diagnoses of sleeping disorders dropped in 2009. An explanation may be that problems with sleeping are often brought up by patients while they are visiting their general practitioner for other complaints. It may be that in such cases the doctor does not register the diagnosis unless a medication is prescribed. Another explanation is that the reimbursement measure was widely announced during the half-year before its introduction. Even patients who did not have a sleeping problem before may have heard that their benzodiazepine medications would no longer be reimbursed and decided not to consult their doctor for troubles with sleeping. We also found a decrease in initiation of benzodiazepine use. An explanation could be that doctors were prescribing benzodiazepines more consciously or that those who were using benzodiazepines were not willing to pay for the medicines themselves.

Furthermore, we found that approximately 50% of the patients received only 1 benzodiazepine prescription. The higher proportion of patients being prescribed only 1 prescription in 2009 indicates that physicians and patients might have become more conscious about the duration of intake, especially in case of sleeping disorder and mild anxiety. The high percentage of single

prescriptions for benzodiazepines in patients with sleeping disorder is in line with the national guideline recommendations of the Dutch College of General Practitioners, which advises that benzodiazepine use should be limited to short courses [7]. That discontinuation rates in patients with sleeping problems were lower in 2009 than in 2008 may be because new users were more determined to have sleeping pills and were willing to pay for them themselves. Patients who were less determined may have chosen not to begin with the sleeping pills at all, whereas in 2008 they may have gone to fill 1 prescription. In addition, it may well be that in 2009 relatively more patients with more severe sleeping problems received a prescription for benzodiazepines.

Two-thirds of the patients had newly diagnosed anxiety coded with *ICPC* P01, “feeling anxiousness, nervousness or tense”; many of these patients might have had mild complaints and most likely would benefit from a short treatment with benzodiazepines. All other patients had their diagnoses coded with *ICPC* P74 “anxiety disorder/anxiety state.” Treatment guidelines for anxiety recommend that treatment of anxiety should be supported by 2 to 4 weeks of concomitant benzodiazepine use, accounting for a single prescription of benzodiazepines [23]. Furthermore, treatment of anxiety is normally a complex process that requires a strong collaboration between the physician and psychologist. In many cases, general practitioners refer these patients directly to a mental health agency, which would explain the relatively high number of patients having just 1 prescription of benzodiazepines and the low number of patients initiating SSRIs treatment in this study [24]. The 16% reduction in overall use of benzodiazepines published by the Dutch Foundation for Pharmaceutical Statistics is in line with the reduction that was found within the LINH database (approximately 18%, data not shown) [25].

Overall, the number of reimbursed prescriptions for benzodiazepines in the Netherlands increased in 2009 by 4.1%. Even so, benzodiazepines disappeared from the top 10 most-prescribed medicines and were among the top 10 medications with the steepest decrease in number of prescriptions (<http://www.sfk.nl>; [www.gipdatabank.nl](http://www.gipdatabank.nl)). This change in ranking suggests that the policy measure has had an effect on the total use of benzodiazepines in the Netherlands.

Careful attention is needed before and after implementing a new policy when determining the effects of regulatory changes. The outcomes of policy changes should be seen in a broader perspective. A regulatory change may lead to public cost savings, but may increase private expenditures or may lead to under-treatment of certain populations. Patients who actually discontinue benzodiazepine use may still need benzodiazepines but may not be capable of paying for these medicines out of pocket, although in the case of daily treatment, costs are low (approximately €12 to €16 per month) [25]. Furthermore, regulatory measures will not always lead to the desired effects [26]. Barbui et al showed that classifying benzodiazepines in reimbursement class C, which means 100% out-of-pocket payment for all patients, was not enough to discourage their widespread use [13]. A study by Wagner et al showed that policies leading to substantial reductions in the use of benzodiazepines did not necessarily lead to other clinical benefits, such as a decrease in hip fractures in elderly [15].

The strength of our study is the large sample size and that we had complete data for each individual patient, including all physicians’ diagnoses and prescription data. Our study focused on the short-term outcomes of the policy. Van Hulten et al showed that 40% patients generally

reinitiate benzodiazepine use within 1 year of discontinuation [17]. Because of the limited follow-up time, we were not able to take prescription restarts into account in this study. Although data for a longer period would be desirable, it would be difficult to attribute changes during a prolonged period to a single intervention, because many patient- and system-level factors change in time.

We did not study prescription patterns for patients with diagnoses for which benzodiazepines were still reimbursed, such as major psychiatric disorders and epilepsy, as a control group, because treatment is often initiated in secondary care, and the number of patients in our database with these diagnoses was limited. Moreover, we were not able to calculate the exact treatment duration. In our study, the duration of each benzodiazepine prescription was set at 30 days. We cannot ignore, however, that some patients might have been using benzodiazepines for a longer or shorter period, which might have influenced the outcomes, especially when looking at discontinuation. The standard treatment duration policy for the first benzodiazepine prescription usually is approximately 14 days. Because we excluded patients with only 1 prescription from our discontinuation analysis, and because the standard treatment duration policy in the Netherlands for each second or consecutive prescription is 30 days, we assume that our results were not influenced significantly. We wanted to observe unwanted effects of the policy, such as substitution effects and effects on health care utilisation. Our primary care database did not include hospital admissions, and with regard to referrals, too many practices had incomplete data. We therefore assessed whether patients with anxiety shifted to treatment with SSRIs. Nevertheless, other treatment options for anxiety and sleeping disorder that are available without prescription were not taken into account and should be investigated. Finally, the proposed regulations for benzodiazepines were released in mid 2008, which gave patients and prescribers time to seek alternative medications and start weaning patients off benzodiazepine use. If we would have been able to take into account only discontinuation based on the regulatory change, we might have found a higher difference in discontinuation rate between 2008 and 2009.

Lessons learned from the evaluation of the effects of pharmaceutical policies in one country may provide important information for policy makers and regulators in other countries. This study showed the effects of the policy on patients with newly diagnosed anxiety and sleeping disorder were (partly) associated with a decrease in benzodiazepine use after the policy change, during which time SSRIs were not substituted for benzodiazepines. Albeit prices for benzodiazepines are low, that benzodiazepines are among the few medications no longer reimbursed may have had a signaling function for patients not to use them.

Reimbursement restriction has led to a moderately positive effect on the decrease in the number of incident diagnoses and initiation of benzodiazepine use in patients with newly diagnosed anxiety or sleeping disorder. At the same time, the proportion of patients receiving prescriptions for benzodiazepines decreased moderately. These findings indicate that in health care settings where no such reimbursement settings exist, physicians have room to reduce benzodiazepine prescribing.

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# CHAPTER 4.2

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## REIMBURSEMENT RESTRICTION ON BENZODIAZEPINES: INFORMATION SERVICES FOR PATIENTS AND THEIR EXPERIENCES

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# ABSTRACT

## Introduction

To assess the patients' perspective on the information services around a reimbursement restriction of benzodiazepine use in the Netherlands.

## Methods

Thirteen community pharmacies recruited benzodiazepine users who received a questionnaire containing items on socio-demographic and health factors, satisfaction of the information services, opinions on and experiences after the policy measure. Logistic regression analysis included age, sex and education level.

## Results

Overall, 372 patients were interviewed, of whom 111 (29.8%) were informed by the media only and 69 (18.6%) by health care professionals only. Respondents informed through their health care professional were more satisfied than those informed by the media (91.3% vs. 73.9%,  $p < 0.05$ ). Younger age (<45 years) was associated with lower satisfaction of the quality of information received (adjusted OR 3.7, 95% CI:1.8-7.4). Sex, age and level of education were not associated with the attitude towards the policy measure.

## Conclusion

Health care professionals play an important role in distributing high quality information to patients on reimbursement changes and their information is highly appreciated by patients. Nevertheless the majority of patients receive their information through the media. Careful attention must be paid to the way patients are informed, and interventions must be tailored to the target professionals before implementing a new policy.

## INTRODUCTION

On January 1st 2009, benzodiazepines were excluded from the Dutch positive reimbursement list when used as anxiolytic, hypnotic or sedative, in order to limit misuse and for cost savings [1,2]. As benzodiazepines were frequently used medicines in the Netherlands (temazepam and oxazepam were in the top 10 list of most prescribed medicines in 2008) and about 30% of the patients using benzodiazepines were chronic users, many patients were affected by this reimbursement restriction [1,3-5]. The restriction had been announced mid-2008 through leaflets distributed by the Dutch government amongst general practitioners (GPs) and pharmacists. In addition, health insurance companies were advised to provide information to their patients either through their website or personal communication. This study assessed patient satisfaction on the information about the upcoming policy measure. In addition, patient opinions on the reimbursement restriction itself and their experiences after this policy measure had taken place were examined.

## METHODS

Pharmacists of 13 community pharmacies belonging to the pharmacy practice research network (UPPER) of the department of Pharmaceutical Sciences of Utrecht University randomly selected patients aged 18 years and older who had been dispensed three or more prescriptions of a benzodiazepine during 2008, of which the last prescription was dispensed in November or December 2008 and who had provided the pharmacy with a telephone number. Patients were excluded if they stayed in a nursing home, had a known history of drug addiction or were terminally ill. The participating pharmacies performed the selection procedure in April 2009. Since the majority of patients in the Netherlands are registered with only one community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription medicines [6,7].

Pharmacists sent letters of invitation that contained information about the study to the patients who fulfilled the inclusion criteria. Patients were asked to inform the pharmacy in case they did not want to participate. Finally, three pharmacy students working on their bachelor research project contacted patients for a telephone interview. The participating patients were given a questionnaire that contained questions on socio-demographic (age, gender, ethnic origin and level of education) and health factors (indication and duration of benzodiazepine use), a measure of satisfaction of the information services and questions on the experiences of users after the policy measure. This study was conducted in compliance with the requirements of the UPPER institutional review board of the Department of Pharmacoepidemiology and Clinical Pharmacology.

## RESULTS

Of the 786 randomly selected patients, 679 received an invitation letter. The remaining patients were not approached on pharmacist's advice (addicted, terminally ill, deceased). Of those that received an invitation letter, 372 (54.8%) patients were interviewed. A total of 258 (69.4%) responders were female. Most responders were older than 60 years ( $n=204$ ; 54.8%), had a low education ( $n=214$ ; 58.0%) and were of Dutch origin ( $n= 350$ ; 94.1%). Sleeping problems were

mostly reported as indication for use (n= 189; 50.8%), followed by anxiety (n= 112; 30.1%) and a combination of both (n= 40; 10.8%).

Figure 1 shows the number of respondents informed and satisfied with the information per channel. Of all respondents, 51 (13.7%) indicated not to have received any information about the reimbursement restriction. The majority of the respondents was informed by the media (n=111; 29.8%). A large proportion of patients was informed through multiple channels (n=89; 23.9%). Health care professionals (including pharmacists and general practitioners) informed 69 (18.6%) respondents, followed by 'other' sources (n=52; 14.0%). 'Other' sources included mostly health insurance companies (n=31; 8.3%).

The majority of the informed respondents was satisfied with the information received (n=294; 79.0%), see figure 1. Those who received their information through their health care professional were more satisfied (n=63; 91.3%), than those informed through the media (n=82; 73.9%) or other sources (n=46; 88.5%). Patients were also satisfied with the information received through multiple channels (n=82; 92.1%). Those informed only through the media were less satisfied than those informed by multiple sources of which at least one was the media (93.7%). This phenomenon was not seen in the other subcategories.

Logistic regression analysis revealed that compared to older respondents, younger respondents (<45 years) were associated with lower satisfaction of the quality of information received (adjusted OR 3.7, 95% CI:1.8-7.4). Sex and level of education were not associated with being more satisfied with the information received.

The majority of respondents did not support the policy measure (n=272; 73.1%). This did not differ substantially between patients being informed by the different information channels.

Lower education (adjusted OR 1.7, 95% CI:0.95-3.1) and age between 46 – 60 years (adjusted OR 1.7, 95% CI:0.95-2.9) tended to be associated with a more positive attitude towards the policy measure, although not statistically significant. Some comments from the questionnaire revealed that patients were worried about the additional costs of benzodiazepine use in addition to the, in their opinion, already high health insurance fees. Others were of the opinion that 'patients in need' should receive the medicines without any (co-)payment. Quotes from respondents supporting

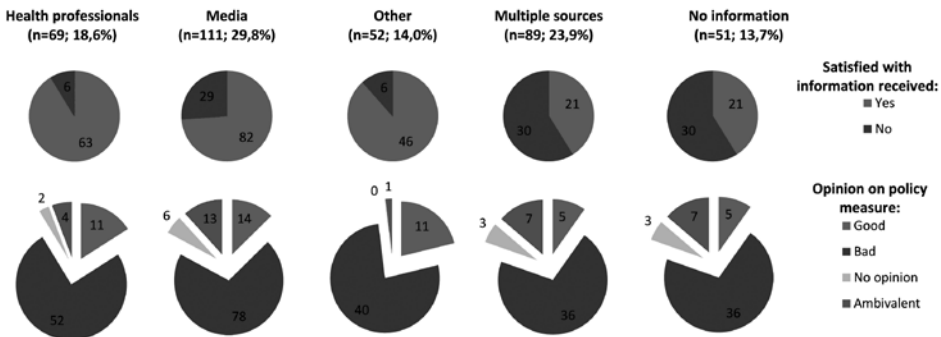


Figure 1 Patients' satisfaction with information received and opinions on policy measure (n=372) by subgroup

the policy revealed concerns about benzodiazepine dependence and even benzodiazepine addiction or the fact that they are not expensive and affordable when really needed.

Of the 372 responders, 286 (85.6%) did not change their consumption pattern, 47 (14.1%) respondents mentioned a lower use of benzodiazepines and only 38 (10.2%) responders discontinued benzodiazepine use after January 1, 2009 (1 person mentioned the reimbursement restriction as cause of discontinuation).

## DISCUSSION

This study showed that more than 85% of the respondents were informed about the reimbursement restriction around benzodiazepines. It also showed that the media informed most people. The Ministry of Health however, in their strategy in providing information to benzodiazepine users, had not directly involved the media. Around October 2008, the Dutch Ministry of Health, Welfare and Sport announced the policy measure through information leaflets distributed to all pharmacies and GPs. In addition, health insurance companies were advised to inform patients about the upcoming regulatory changes. The 'early' distribution of information through health care professionals gave patients and health care professionals time to seek for alternatives and to start tapering off benzodiazepine use. The high satisfaction on the information received through health care professionals (and health insurance companies) showed that these sources were functioning properly, however it should be noted that the health insurance companies played a minor role in the distribution of information. Respondents with a low level of education had a tendency to have a negative attitude towards the policy measure. This should be taken into account when implementing such a policy as benzodiazepine use is generally higher in people with a lower social economic status [8,9]. Although still more positive than negative, respondents were least satisfied with the information provided by the media. Younger people were found to be less satisfied with the information received than older people. Since there has been continuous growth in access and use of media by younger people this might be a possible explanation of the lower satisfaction found among younger people [10]. Governments, but also health care professionals should get a realistic understanding of what role media will or might play in the distribution of health services information. Besides it is of utmost importance that the information provided by the media is in line with what health care professionals and government are aiming at and health authorities should be aware of this.

Views of the general population on the policy measure were reflected by data provided by the Dutch Health Care Consumer Panel (May 2009). This Panel (subsidized by the Ministry of Health) consists of 2800 Dutch individuals who represent the Dutch population. As a response to the question whether the costs for benzodiazepines were reasonable, 48.2% responded that the costs were low versus 38.6% high. The remaining respondents had no opinion [11].

Recent publications show a decline in benzodiazepine use after the implementation of the policy measure [3,12]. This suggests that the reimbursement restriction has had an effect on the total use of benzodiazepines in the Netherlands. Our study showed that only a small number of responders discontinued benzodiazepine use because of the policy measure. This finding

and outcomes of other literature show that the decrease in use has been mainly caused by a lower initiation of benzodiazepine use and a lower number of people being diagnosed with symptoms for which a benzodiazepine may be prescribed [2,6,12].

In conclusion, this study showed the importance of evaluating information services around policy measures. It confirmed that health care professionals play an important role in distributing high quality information to patients and their information is highly appreciated by patients, nevertheless the number of people informed through this channel was remarkably low. Attention must be paid to the various information services and strategies must be developed for patients not being adequately informed. It furthermore shows that media play at least an important role as health care professionals in informing the public. When designing a new policy, health authorities should actively involve, educate and entrust the media with essential health information, which may then be relayed to the public in readily accessible formats. In short, careful attention must be paid to the way (specific) patients are informed, and interventions must be tailored to the target professionals before implementing a new policy.

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# CHAPTER 5

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GENERAL DISCUSSION



## INTRODUCTION

There are more (effective) medicines today on the market and available therapies than ever before. Patients (in Europe) have great expectations of health care and regularly access multiple health care services. Yet, medicines are frequently not used to their full potential or according to generally accepted criteria. Not all prescriptions are necessarily based on patients' needs and their needs are not necessarily met by therapy with medicines. Consequently, there is as much concern about inappropriate and expensive prescribing as there is about under-prescribing [1]. The utilisation of medicines is defined by the World Health Organization (WHO) as the "marketing, distribution, prescription, and use of medicines in society, with special emphasis on the resulting medical, social, and economic consequences". The development of the utilisation of medicines as a research area facilitated the study of medicines prescription and usage in a scientific and formal manner [2].

This thesis includes studies on cross-national variation in medicines use from a pharmaceutical system perspective. The level of medicines use in various countries and across multiple medical conditions is measured, while also taking pharmaceutical system factors into account.

## MEDICINES UTILISATION STUDIES – HISTORICAL DEVELOPMENT AND THE CURRENT LANDSCAPE

### Evolution of medicines utilisation studies

The beginning of medicines utilisation studies can be traced back to the early 1960s [3]. Serious consideration was first given to studies of medicines utilisation during a symposium on medicines toxicology organized by WHO in Moscow, in 1964 [3]. Medicines utilisation had been sparked by the thalidomide disaster that had inspired many other developments in the health care sector at the time. People came to realize that if they had no idea of the scale by which (and the manner in which) such dangerous products had been employed, they would not be in a position to assess the risk frequency or location. The Moscow meeting led to a study on medicine consumption in six European countries between 1966 and 1967, which showed significant variance in the use of medicines [1]. This study was followed by a symposium entitled "The consumption of drugs" in Oslo, in 1969, that clearly confirmed that an internationally accepted classification system was needed for presenting data on medicines consumption as well as a technical unit of comparison in medicines utilisation studies. As a consequence of this symposium, a small group of scientists came together and developed the anatomical therapeutic chemical (ATC) classification system for medicines as well as the defined daily dose (DDD), a comparative unit of medicines use that was robust across therapeutic classifications, dosing forms, and diverse populations [4].

Since then, the focus of medicines utilisation activities has clearly evolved. Initially, the main focus was to observe variation in medicines use among countries and to improve medicines utilisation through cross-national medicines utilisation studies based on the ATC/DDD methodology [5]. These studies revealed large differences among and within countries

that could not easily be explained by differences in the prevalence of morbidity alone [4,5]. These findings led to the expansion of the research area to include social, economic, and qualitative methods for studying medicines utilisation and resulted in a more generalized public health focus [3,7]. The research subsequently shifted from being merely descriptive to being outcome- and quality-oriented, and thus making it possible to identify, for example, high-cost prescribers or those using an extraordinary quantity or proportion of certain products [8]. An important contribution to this research was the development of medicine use (prescription) quality indicators. Indicators are quantitative measures, often expressed as rates, ratios, or percentages, and include or imply a numerator and denominator. Together with other tools for monitoring the quality and performance of health services, these indicators can contribute to the planning, management and evaluation of medicines utilisation [9]. The indicators are being used for quality improvement initiatives, e.g. to measure whether the right medicines are prescribed to the right patients and to identify and reward prescribers who meet predefined standards of quality [4,10]. Examples are the measurement of the prevalence of antimicrobial medicine self-medication or the assessment of the quality of diabetes care [11,12].

However, within a particular health care system, a specific treatment might not always be operationally feasible and there are many legitimate reasons for deviating from the recommended treatment [12]. After all, a large number of other factors exist that influence the prescribing of medicines and at the end of the day these may cause variation in the use of medicines among individuals, regions and/or countries. For example, a country that spends more on healthcare or a country that has few controls on prescribing can be expected to have a higher level of medicines consumption. Hence, medicines utilisation in optima forma must be studied in the full context using (quality) indicators where necessary, but always including the contextual environment of medicines utilisation.

In the last decade, an increasing interest has been seen in studying (variation in) medicines use in an integrated way. This approach includes combining all relevant processes and regulations within a pharmaceutical system that may cause cross-national variation in medicines use. The publication of several recent (international) studies towards the extent and causes of international variation in the use of medicines reflects this change [13-15]. The aim of this type of research is to understand variation in the context of various health care systems and to assist in the development of best practices and optimal pharmaceutical policies that will ultimately lead to optimal and affordable health care for all. This interest does not only stem from policy makers, but also from the public. For instance, national patients' associations can lobby for changes by referencing the level of access to medicines in other countries. Furthermore, giving the public insight into cross-national variation in medicines use and the challenges governments and health care providers face in providing safe, affordable and effective medicines will hopefully lead to better understanding of the variations in restrictions to access or availability of medicines in one's own country.

Despite the acknowledgement of the relevance of these types of studies, there is little literature on cross-national variation in medicines use, including both data on medicines usage and data on important factors of the pharmaceutical system—the environmental context. After

all, there are many (technical) challenges to measure the levels of medicines usage in various countries and across multiple medical conditions taking into account the pharmaceutical system factors. This thesis accepted the challenge and presents aggregated data (data not on individual patients) on major features of national pharmaceutical systems, accompanied by actual usage data from various countries and across multiple medical conditions on either a global or European level. However, some issues on medicines use, such as the impact of a specific policy measure, were studied in a single country and used patient data because of the purpose of the study (measuring the effect of a single policy) and available information. Lessons learnt from the studies in this thesis and methodological issues and challenges of these findings will be discussed. Areas for future research are identified to further improve our understanding of cross-national variation in medicines use in a full context.

## LESSONS LEARNT FROM STUDIES IN THIS THESIS ON CROSS-NATIONAL VARIATION IN MEDICINES USE

### **International overview of national medicines policies and medicines use**

Regulating the pharmaceutical market is complex and involves a dynamic interplay among government and multiple stakeholders, and not simply the prescribing physician [16]. The decision-making context becomes more uncertain and unpredictable especially in cases of a level shift, from an individual-clinical to a population-policy level [17]. Since there are many incentives to regulate the demand side of the pharmaceutical market, there are many key health-system stakeholders involved in these decisions, such as policy makers, payers and health care professionals [18]. Pharmaceutical policy-making is a challenge due to conflicting interests between key stakeholders, just as it is a challenge to improve public health with limited resources [19]. Stakeholders with conflicting interests and the agreed-upon outcomes may ultimately lead to a variation in medicines use. A key step in regulating the pharmaceutical sector within a national health system is the development of national policies, which may or may not be collected in a single document—a national medicines policy (NMP). Chapter 2.1 focused on national medicines policies around the world. It showed that countries' recognition of the importance of having a NMP increased over time, especially in high-income countries. Nevertheless, not all countries have a NMP, since political pressure by national experts or non-governmental organizations is often needed to establish a single comprehensive document as shown by the case studies included in this chapter. The development of a NMP is clearly an example of a macro-level development—a cooperative endeavour—in which various stakeholders (prescribers, dispensers, and consumers, as well as those who make, market, distribute and sell medicines) come together and political dynamics are considered. A NMP should account for elements of social and economic policy and result in better health outcomes for all citizens, thereby focusing on people's access to medicines and responsible use of medicines in particular [20,21]. A country's NMP may be quite similar to a NMP from other countries, but the initial local situations vary and so the policies will likely differ in emphasis and how best to address problems [22].

As outlined in Chapter 2.1, countries must choose the elements that are most relevant and realistic in their situation given the available human and financial resources. The case studies demonstrated that the policy process is as important as the policy document, since the process creates a mechanism for stakeholders to come together and collective ownership of the final policy can be achieved. This process is crucial in view of the challenges to NMP implementation and monitoring, because policy-making does not stop after the NMP is developed. This is demonstrated by a global case describing the withdrawal of a COX-2 (cyclo-oxygenase-2) inhibitor and well documented in Australia. Australia's NMP aims to include quality use of medicines [23]. However, similar to many other countries, the policy stakeholders failed to protect Australians in this case. Regulators did not appropriately warn prescribers about the potential cardiovascular risks of COX-2 inhibitors and the Pharmaceutical Benefits Scheme did not limit unjustified expenditures on the medicine. Furthermore, the pharmaceutical companies ran intense and misleading promotional campaigns on COX-2 inhibitors without adequate controls. Lessons learned from this case were that core elements of the Australian NMP—in particular the medicines approval process, the post-marketing surveillance system, the control of promotion, and the quality of independent information—required major reappraisal to avoid similar cases in the future. Furthermore, it emphasized that monitoring and evaluation is an important aspect of every NMP, and that developing an optimal NMP for one's own country is a continuous learning process.

Chapter 2.2 examined global medicines use by volume within the outpatient sector. Usage patterns across 84 countries in all income categories and with a variety of healthcare systems were described. This chapter showed that medicines use has grown in countries across all income categories. The percentage of growth was higher in low-income countries than in high-income countries, although in absolute terms, the picture was reversed. Medicines to treat chronic diseases were a larger proportion of total volume in the outpatient sector over time. Projections indicated that chronic disease medicines volumes would need to increase dramatically if access is to be provided to those who need them. A previous study demonstrated that this might pose a challenge to low- and middle-income countries since the availability of medicines for chronic conditions is often poor [24]. The results in Chapter 2.2 also show that the usage of medicines included on the WHO Model List of essential medicines was similar across countries of all income categories and was approximately 25-35%. Higher country income was not associated with disparate use of the WHO Model List products, and out-of-pocket expenditures were not necessarily associated with lower usage rates. IMS Health data (a sales database containing data from the private and public sector depending on the country) were used in this chapter for two reasons: first, ease of use and comparability and second, the need to look at long-term trends. Long-term trend information has often not been collected from the public sector in many middle- and low-income countries. This may be because the public sector reimbursement of medicines, particularly those used outside the hospital, is a relatively new phenomenon in many countries [25]. Thus, the IMS data are often the only source of data on medicines consumption in earlier periods. The focus of this chapter was on medicines use outside the hospital. This is not because the hospital sector is unimportant, but rather because the volume information in



the hospital sector is often unavailable at least within high-income countries, and even within commercial databases. Despite giving valuable information on the variation in medicines use across a large number of countries and income categories, the analyses in this chapter further underline that studies on a macro level will benefit from an improved comprehensive data collection that covers both public and private sectors and the in- and out-patient setting.

### Understanding variation in medicines use in Europe

As shown by our studies in Chapter 3, variation in medicines use is driven by a multitude of factors that may vary among countries and therapeutic areas.

Chapter 3.2 showed that utilisation of Tumour Necrosis Factor Alpha (TNFalpha) inhibitors varied widely from 0.32 (Portugal) to 1.89 (Norway) DDDs/1000inhabitants/day (2007). Various factors were assessed as possible explanations for the differences seen in use among the four countries included in this study. Examples are pharmaceutical system factors (such as the time lag between market authorization and market launch), total pharmaceutical expenditures per capita, and initial reimbursement dates and outcomes. Furthermore, country characteristics, guidelines and price information were also taken into account.

Finally, four key leading rheumatologists from each participating country were interviewed to comment on the differences seen in utilisation according to cultural context and clinical attitude towards TNFalpha inhibitors. This study showed that the country's total health expenditure seemed to be a major driver for the utilisation of TNFalpha inhibitors ( $R^2=0.81$ ). Virtually the same correlation was found when looking at GDP. These results were supported by data published by Jönsson et al. (2008) who also noted differences in national income as a possible reason for the much lower use of these medicines in central and eastern European countries compared with western Europe, Canada and the United States [26]. When interpreting these results, one should realize that the medicines included in this study are biologicals. In general, biologicals are more expensive (a result of the high cost of development and production, and few patent expiries) than small molecule medicines, such as aspirin or ibuprofen [27]. Therefore, it is not surprising that total health expenditure may be the driving force behind the differences seen in the utilisation of such medicines. However, for small molecules medicines this might not be the case. This study also showed that additional drivers, such as patients' access to specialists, cause variation in the use of these medicines. Finally, the differences in preferences for the various TNFalpha inhibitors across the countries included in this study are also noteworthy. Portugal seems to be the only country where infliximab (to be administered as intravenous infusion in hospitals) was used more frequently compared to etanercept and adalimumab (both to be injected subcutaneously and typically by the patient at home). An explanation can be found in the organization of the national health care system, since patients in Portugal are required to go the hospital for treatment with these medicines, whereas in other countries there are already systems in place to deliver etanercept and adalimumab in the patients' homes.

The emphasis of Chapter 3.4 was on cross-national variation in the duration and outcome of reimbursement decisions and their implications for patients' access to three new psychotropic medicines in European member states, supported by five-year consumption data on these medicines.

Variation in Europe in the average number of days from reimbursement application to decision has been shown by the OECD Pharmaceutical Pricing Policies in a global market report (OECD 2008) [28]. Our study examined the effects of ‘delayed’ reimbursement decisions on the uptake and level of use of new medicines by adding usage data to reimbursement duration and outcome data. Although variation in use was already expected to occur, due to differences in opinions and perspectives of the prescribing physician and/or user, this study showed the additional impact of the time taken for a reimbursement decision on the level of use of new medicines, even five years after market authorization. Regulators should realize the impact of the above-mentioned findings when deciding about reimbursement, and researchers should take the effect of reimbursement decisions and ‘delays’ into account when explaining causes of cross-national variation in the uptake and level of use of new medicines.

In the field of cross-national comparison of medicines use, healthcare researchers may benefit from investigating other areas of society. For example, a country’s culture is an important factor in a health care system and should also be considered when conducting comparative studies. After all, culture affects the behaviour of a country’s population and benchmarking the level of medicines use in one country against another with a dissimilar culture may be ineffective. And although international comparative research does acknowledge culture as an explanatory variable, there is very little empirical material to rely on. Most research on medicines use and culture has been performed as explanatory studies using surveys that were circulated among experts or citizens [29]. Geert Hofstede was one of the first to quantify cultural dimensions based on extensive research to explain observed differences between cultures. His theory of cultural dimensions, as used in Chapter 3.3, describes the effects of a society’s culture on the values of its members, and how these values relate to behaviour using a structure derived from factor analysis [30]. The theory has been validated and widely used in several fields as a research paradigm, particularly in cross-cultural psychology, international management, and cross-cultural communication [31]. Despite being validated, little is known about the utility of this model for assessing the relationship between culture and medicines use. To our knowledge only two other studies have used Geert Hofstede’s theory to assess the effect of cultural diversity in the use of antibiotics [32,33]. In our study, cultural diversity had little effect on the uptake and use of three relatively new psychotropic medicines. Reasons for this outcome could be that the number of countries was (still) limited and the study may therefore have been underpowered to detect significant differences among countries. The results may also be due to the fact that cultural diversity does not play an important role in explaining cross-national variation in new psychotropic medicines use, or that Hofstede’s model is unsuitable for new medicines just entering the market. More research should be done in this field to explore the utility of Hofstede’s model for explaining cross-national variation in medicines use. Perhaps, other culturally differentiating approaches may be used to assess the impact of cultural diversity on medicines use, such as religion; e.g. Protestant versus Catholic countries or tradition [7,34,35].

Sofar, the studies in this thesis have tried to understand cross-national variations in medicines use by accounting for pharmaceutical system factors. However, the level of medicines use within a country may also impact the organization of the pharmaceutical system. The rationale

for conducting the exploratory study in Chapter 3.5 was to open the debate on this issue. With the establishment of the European Medicines Agency, an important achievement has been made in the harmonization of the work of existing national medicine regulatory bodies. This study however, showed a great variability in contributions of individual EU member states to the pharmaceutical regulatory system. In addition, usage data of medicines authorized in 2004 showed substantial variation in uptake and usage level among EU member states. This may be the result of EU member states' responsibility for the way they build and fund their national health care systems. The finding that for some countries the variability in contributions to the pharmaceutical regulatory system goes hand in hand with the variability of actual prescribing and usage calls for a discussion about the sustainability of the regulatory network that depends heavily on European partnership and community responsibility. A regulatory network is more likely to blossom in an environment where the work is shared to bring new medicines to the market and pays off in safeguarding patients' interest on a national level as well.

### National level studies

Chapters 4.1 and 4.2 focused on a specific policy measure in a single country (the Netherlands). This measure included the removal of benzodiazepines from the Dutch reimbursement list for use as an anxiolytic or hypnotic. Highly aggregated data by the Dutch Foundation for Pharmaceutical Statistics (SFK) had shown an overall reduction in national use of benzodiazepines after the introduction of this measure [36]. However, the specific cause of this reduction remained unknown: did chronic users discontinue use, was there a decrease in the number of people initiating use, and which specific patient population was affected? In Chapter 4.1 the impact of this reimbursement restriction on a subpopulation (patients with newly diagnosed anxiety or a sleeping disorder in general practice) was assessed on a patient level to obtain more detailed insight into the dynamics shown by the aggregated data on a national level. It turned out that the reimbursement restriction led to a moderate decrease in the number of incident diagnoses and initiation of benzodiazepine use in this group of patients. Although the individual effects (e.g. decrease in the number of diagnosis and the initiation of benzodiazepine use, increased number of discontinuers) were moderate, accumulation of these effects might be a possible explanation for the trend in the data from SFK. Chapter 4.2 specifically addressed the importance of information services for the same policy measure. This study showed that careful attention must be paid to how patients are informed. Users of benzodiazepines were most satisfied with the information received from their health care professional. Nevertheless, most patients were informed by another means—the media. Both studies used individual data on a patient level. This approach usually concentrates on the individual patient or physician choices without explicitly accounting for the institutional context. Usually, the aim of studies including micro-level data is not to compare medicines use in various countries, but rather to find explanations for medicines use within a certain setting and the results may contribute to optimal evidence-policy making. It remains difficult to compare the effects of specific policy measures in various countries when no similar, preferably identical, measure regarding the same medicines and same restrictions exists. Databases including similar variables should

exist to study the impact of a particular policy measure in a specific patient population across multiple countries. Patient-level data may be a useful addition to studies with aggregated data. These data can provide an answer to specific questions that remain unanswered when using only macro-level data. After all, the consequences of a policy measure can be particularly severe or have substantial unintended effects in specific patients groups and therefore, monitoring the effects of a policy measure is warranted [37].

## METHODOLOGICAL ISSUES IN MEASURING VARIATION IN MEDICINES USE

Various methodological issues influence the measurement of variation in medicines use and generate uncertainty, discussion and debate. This paragraph focuses on the methodological issues raised by and encountered in the studies in this thesis.

### Identification of potential data sources for comparative association studies

Medicines utilisation data can be sourced from databases that are commercial (e.g. IMS Health sales data), administrative (e.g. databases containing claims, prescription or dispensing records), or from regulatory agencies, suppliers or practice and community settings. It may be redundant to mention that the database used should be suitable for the type of research undertaken [38]. Various types of information on medicines use are required depending on the question being asked [39]. This information includes overall medicines use, or use of medicines in a specific subpopulation, individual generic compounds or specific products. Often, information about the condition being treated, the patient or the prescriber may be required as well [40].

Ideally, for comparative association studies (linking medicines utilisation data with pharmaceutical system factors), a single database for studies on medicines utilisation by volume could provide data:

- On actual prescribed and non-prescribed medicines (OTCs)
- From the in- and out-patient setting
- About the entire population (or a recognized random sample thereof)
- Regardless of payer or source of finance (public, private, out-of-pocket)
- Using standardized definitions of utilisation
- With actual counts of unique claims
- That permits flexible aggregation of data based on stratification variables such as age groups, gender and geography
- That covers indications of use
- That complies with the highest standards related to privacy, confidentiality and security requirements

Unfortunately, a single comprehensive (administrative) national database that reflects the above needs is currently not available. Nevertheless, some databases such as the Netherlands Primary Care Research Database (NPCRD) (used in Chapter 4.1) or the UK Clinical Practice Research Datalink contain most above elements, but only for a single country [41,42]. For a

cross-national analysis, researchers must rely on either (highly) aggregated data or link various (national) databases. Aggregated data has been used for the majority of cross-national comparative studies in this thesis. In general, these data have less detailed clinical content, but allow for comparison among multiple countries each with their own specific database. Chapters 2.2, 3.3 to 3.5 include only the sales data from IMS Health. However, other cross-national comparative studies in this thesis use various (national) data sources, such as sales data from Institutes of Public Health, collaborations between pharmaceutical companies, importers and wholesalers, claims data, ambulatory or dispensing data (Chapters 3.1 and 3.2). In some countries, as shown in chapters 3.1 and 3.2, data on a national level was not available from a single data source. The combination of an in- and out-patient database in the Netherlands was necessary to obtain national utilisation data on biological; TNFalpha inhibitors were used as a case study. Linking multiple data sources is a possible solution as shown in these studies. Linked data may have potential for policy-relevant research since they can be obtained locally, are cost-effective, timely, may contain clinical content variables, and are obtained from the “real world”. Chapter 3.1 specifically focused on the challenges and issues of collecting national medicines utilisation data for biologicals. This study showed that the characteristics of the medicines under study (usage settings and distribution procedures to patients, e.g. home deliveries versus in-patient use) and databases (type of data collected, public availability and data sources) influenced the way data were collected and determined the type of research and policy questions that could validly be addressed. Furthermore, this study showed that there is room for improvement since the required data on national TNFalpha usage in the European countries included in this study, was not easily accessible—if at all.

### Units of volume measure

Volume data on an aggregated level were used to compare the large number of countries in this thesis. Whilst analysis of information on expenditures may also be interesting, expenditure information does not provide a complete picture of consumption since prices vary widely for the same product across countries, over time and under varying circumstances [43].

The ability to compare medicines utilisation across populations, geographical locations and over time requires standardized information [39]. Medicines utilisation can be quantified by a variety of volume measures, including the number of claims (or prescriptions filled), number of specific medicines, quantity dispensed, prescribed daily dose (PDD), defined daily dose, and the IMS Health Standard Unit (SU). Unfortunately, none of these measures alone gives a complete picture of medicines utilisation; however, used in combination they may serve to address a variety of questions. The following paragraph elaborates on the two measures used in the studies included in this thesis.

The DDD is the assumed average maintenance dose per day for a medicine used for its main indication in adults and does not necessarily reflect the recommended or actual dose used [5,44]. For some medicines, DDDs have not been assigned because it is difficult to determine appropriate DDDs. For example, for infliximab (studied in Chapter 3.1 and 3.2), the concept of DDDs has important limitations since the dose is weight-based, differs according to indication

and there are frequent dose-escalations and changes in the infusion interval. For these studies, however, we assumed that these differences would occur in all studied countries and therefore would not influence the trend of medicines use. But when the assessment of reliable utilisation rates is the main goal of a study, the potential issue of assigning accurate DDDs should be taken into account. Furthermore, it is important to note which version of the index is used in the calculations, particularly if comparisons are made over time (as in the studies included in this thesis) since WHO can alter the ATC and DDDs [5].

The PDD is more precise than the DDD. The PDD is defined as the average dose prescribed according to a representative sample of prescriptions. Although PDDs are relevant for cross-national comparative studies, they are used less often since they may vary among countries. This may also be true because PDDs are less frequently available and require patient level databases [44,45].

The number of dispensing units (tablets, inhalers, packages, grams, litres, etc.) can be used for quantifying medicines utilisation. IMS SU can be applied only when the use of a single medicine or a well-defined product is evaluated [25]. Counting dispensing units has limitations. For example, tablets of the same medicines may come in various strengths and thus it is inappropriate to combine them when merely summing the number of tablets. In addition, the same medicines may be available in various dosage forms (e.g., tablets and liquids) thereby precluding a roll-up.

The two systems (WHO DDD and IMS SU) should be seen as complementary. Each has been developed for a particular purpose, but both allow comparisons of volume or medicines consumed. The IMS SU was presented in Chapter 2.2, whereas in all other studies, WHO DDDs were presented. For Chapters 3.2, 3.3 and 3.4, data in SU from IMS were converted to WHO DDD data formats. The WHO DDD system is widely used internationally and this makes it easier to compare the findings in this thesis to other findings in the literature. The conversion to DDDs was done at a molecule level, taking the pharmaceutical form and the strengths, quantities or volumes within each pack into consideration.

### **Role of additional data in pharmaceutical policy analysis – data enrichment**

Data enrichment of aggregated data should be seen as a value-adding process, where external data from multiple sources is added to the existing data set to enhance the quality and richness of the data. This process may provide more information on (cross-national variation in) medicines use in a full context due to the ability of enhancing the understanding of the regulators', prescribers', pharmaceutical industries', and patients' behaviour in their "natural environment", and to also enhance the validity of the quantitative findings. For example, adding costs to usage data in DDDs and comparing usage (e.g. consumption in a hospital) over time, allows us to say that yes, expenditure is higher, but the number of DDDs has not changed significantly. This means that there has been a shift towards more expensive and probably newer medicines for the same indication [46]. There are many types of data that can be added to aggregate data. Qualitative data from interviews (Chapters 2.1 and 3.2), survey data (Chapter 3.3, 3.4 and 4.2), and variables of the pharmaceutical system, such as reimbursement decisions and dates, guidelines and launch dates (Chapters 2.2, 3.2 and 3.4) have been included in this thesis. Chapter 4.2 clearly

showed how survey data may be used for assessing patients' attitudes and beliefs and how these change over time. Chapter 3.2 highlighted the added value of qualitative data. Interview data revealed further explanations for the differences in medicines use that could not be explained by quantitative data, such as recognition of the low numbers of prescribing physicians.

## IMPLICATIONS OF THE FINDINGS AND OPPORTUNITIES FOR FUTURE RESEARCH

With the increasing importance of knowledge about the context in which medicines are being used, studies like this thesis will become more important. The thesis identified two critical factors for performing a successful study on the extent and causes of cross-national variation in medicines use from a pharmaceutical perspective. The first important actions for future research are to improve data harmonization and combine data(sources). Analysis of patterns of medicines use is complicated by the diversity of databases and classification systems. Whilst the various systems can be viewed as complementary, patterns of medicines use and the impact of the pharmaceutical system would be clearer if data from various sources were combined. By comparing and combining datasets, researchers may detect more subtle and complex associations among variables, which in the end may improve the interpretation of variation caused by historical and societal developments—the contextual environment. Governments can play an important role in data collection and harmonization; every national medicines policy should ideally contain a comprehensive plan to collect reliable medicines consumption data. The strategy to achieve this should be outlined in the NMP.

More advanced analysis techniques may need to be used, such as the multi-level analysis in Chapter 4.1. Multi-level analyses allow for the inclusion of indicators at both an aggregate and individual patient level. As such, the effect of both the national or institutional context and the individual characteristics of medicines utilisation outcomes can be estimated in one analysis. For better harmonization of data, close collaboration between regulatory authorities, pharmaceutical industry, research associations and academia is necessary, since the required data is often collected in large databases that are owned by single institutes (for example, independent research associations). An example of an international data sharing and stakeholder collaboration is the public-private PROTECT project [47]. PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) is a collaborative European project that addresses the limitations of the current methods in the field of pharmacoepidemiology and pharmacovigilance. The EMA is the coordinator and Glaxo Smith Kline is the deputy co-ordinator of PROTECT. They manage a multi-national consortium of 33 partners including academics, regulators, small and medium enterprises, the European Federation of Pharmaceutical Industries and Associations (EFPIA) companies [47].

Adequate information on the environmental context is crucial for a better understanding of variation in medicines use, and the second identified important action for future research. In the last few years, some large-scale European projects have focused on understanding the pharmaceutical system and have produced (pharmaceutical) indicators for comparative purposes.

The Pharmaceutical Pricing and Reimbursement Information project (PPRI), for example, collected information on pharmaceutical systems in all 25 EU member states with an emphasis on pricing and reimbursement [48]. In addition, they developed a set of pharmaceutical core indicators for comparing pharmaceutical systems that were filled with real data from various countries. Input for this project was largely obtained from the PPRI network with more than 60 members who were mainly competent authorities and third party payers from a total of 38 countries. Input from this project and network was used by Leopold et al. (2012) in a study that illustrates the importance of understanding the pharmaceutical policy context. This study focused on the various interests taken into consideration by national governments when shaping a national pharmaceutical policy [49]. It showed that external price referencing (EPR) is a cost-containment tool that is used in 24 of the 28 EU countries. However, the EPR systems in place in these 24 countries showed significant differences that can only be fully understood through individual contacts with the PPRI network members. In particular, the composition of the reference baskets that were used varied considerably. The authors suggested that the methodology that the EPR system applied might have effects on the access to and level of reimbursable medicines. Unfortunately, no usage data were included in this data to support that suggestion.

Another example of the acknowledgement of the importance of understanding the (pharmaceutical) context is shown by the launch of the first global strategy on research into health policy and systems by WHO at the Second Global Symposium on Health Systems Research in Beijing (November 2012) [50]. The strategy called for a more prominent role for this research, as many countries are aiming to strengthen their health systems and develop universal and equitable health coverage. The global symposium focused on the current state of health systems research including research collaborations among various sectors of academia and policy making, the development of robust methods to assess the effects of healthcare reforms, and the use of this research to accelerate countries' uptake of effective universal health coverage.

For a good understanding of the environmental context, it is important to keep in mind that causes of cross-national variation differ across types of medicines and countries, and this means that each pattern has a specific dynamic. It is essential to hypothesize why certain pharmaceutical system factors may influence medicines use, and by which mechanism. Our study, for example, showed the relevance of gaining insight into a country's wealth since the results showed that GDP played a significant role in explaining cross-national variation in the utilisation of biologicals. This might not be the case for small molecules. Much can be learned from (methods in) international comparative studies in other research areas, such as sociological and economic studies, as shown by our study that included Hofstede's dimensions of national culture to assess a possible relationship between cultural diversity and the level of medicines use.

Finally, at a recent Ministers Summit (October 2012), with the theme "The benefits of responsible use of medicines", it was shown how highly aggregated data (as used in this thesis) can be used for policy-relevant questions. The Summit was organized by the Dutch Ministry of Health, Welfare and Sports in the context of the International Pharmaceutical Federation (FIP) Centennial. The purpose of this Summit was to explore solutions to improve patient outcomes and support sustainable and cost-effective health care. An important role in providing evidence to this Summit



was played by IMS Health, who provided their (highly aggregated) data since the issues being addressed in this Summit could not be answered with studies that used data from only specific subpopulations or when the resources for a detailed study at the patient level was not be available.

## FINAL CONCLUSION

The outcomes of medicines utilisation studies can play a key role in helping to understand, interpret, evaluate and improve the prescription, administration and responsible use of medicines. Many key stakeholders find that these studies are valuable since the results are used to foster a more efficient use of scarce health care resources. In addition, dissemination of the outcomes of these types of studies among the general population may lead to a better understanding of the existence of restrictions on access to or availability of medicines in one's own country. The studies in this thesis have shown that the current available databases and epidemiological methods provide ample opportunities for studying cross-national variation in medicines use from a pharmaceutical system perspective. However, much work remains to be done, especially in data harmonization and understanding the full pharmaceutical context.

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# CHAPTER 6

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SUMMARY AND SAMENVATTING



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# CHAPTER 6.1

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ENGLISH SUMMARY





## SUMMARY

Access to effective and affordable medicines (medical care) is considered an equitable right for all (European) citizens. Ensuring access to medical care is a challenge for governments and health care systems across the world. Health care systems and, as part of that the pharmaceutical care systems, stem from specific political, historical, cultural and socio-economic traditions. As a result, the organizational arrangements for health care differ considerably among European Union (EU) member states - as do capital and human resource allocation. Furthermore, policy makers across European countries may make distinct decisions to guarantee their population (affordable) access to medicines, physicians make patient-specific decisions in their choice between treatment options and patients often vary in their treatment-seeking decisions. As such, variation in the uptake and level of medicines use is a natural consequence of each EU country's system. This thesis aims to gain insight into the cross-national variation in medicines use in the EU. The level of medicines use is measured across several medical conditions and in multiple countries. Finally an analysis is presented of various pharmaceutical system factors that may explain cross-national variation in medicines use. The outcome of these studies are therefore of major interest to all stakeholders in the health care system when it comes to making medicines available.

In the introduction (**Chapter 1**) we describe variation in the uptake and level of medicines use across countries. Previous studies focusing on variation in medicines use, have shown a (wide) variation in the level of use of various medicines and across different countries, e.g. variation in the outpatient use of antibiotics. Single causes of variation in medicines use are often difficult to identify as various elements such as cultural or organizational aspects may play a particular role. In addition, it is likely that any given level of use of a specific medicine in one country is determined by a set of factors that might vary in another country. Most studies so far focus on cross-national variation in medicines use, but others focus solely on the variation in pharmaceutical system factors, such as pharmaceutical policies. These variations (in pharmaceutical system factors) may (possibly) lead to cross-national variation in medicines use, but this has rarely been studied so far. However, in the last decade, the importance has been recognized of and an increasing interest has arisen in studying variation in medicines use in an integrated way, including the combination of all relevant pharmaceutical system parameters. The studies in this thesis add to this and present aggregated data on major features of the national pharmaceutical systems accompanied by actual usage data from multiple countries and across various medical conditions on either a global, European or national level. The findings in this thesis are placed into three categories: global overview of national pharmaceutical policies and medicines use, understanding variation in medicines use in Europe and monitoring a specific policy in a single country. As such, this thesis aims to guide future analytical work to better understand the extent and causes of variation in medicines use leading to better insights and policies in this important sector of modern life. The approaches and discussions as described in this thesis can be used as a start and will hopefully contribute to making evidence based and justified decisions on optimal medicines use in the future.

In **Chapter 2** we present a global overview of variation in existing national medicines policies and pharmaceutical consumption. A National Medicines Policy (NMP) is a (collaborative) commitment to goals in the pharmaceutical sector and a guide for action. It expresses and prioritizes the medium- to long-term goals set by the government, and identifies the main strategies for attaining them. **Chapter 2.1** is a historical review of the process of NMP development within health care systems as it occurred over the last 25 years worldwide. The increase in number of NMPs is seen across all national income categories with the greatest rise in recent years in high-income countries. Nevertheless, not all countries have a NMP since political pressure by national experts or non-governmental organizations is often needed to establish a single comprehensive document. This chapter also includes four examples of a NMP formulation process. They show that a political window of opportunity usually serves as a key element in reforming a NMP. Furthermore, the case studies demonstrate that the policy process is as important as the policy document, since the process creates a mechanism for stakeholders to come together and collective ownership of the final policy can be achieved. This may be crucial in view of the challenges to implement and monitor a NMP.

**Chapter 2.2** examines global medicines consumption by volume within the non-hospital sector. Usage patterns across 84 countries in all income categories and with a variety of healthcare systems are described. The results show that consumption has grown in countries of all income categories. The percentage of growth is higher in low income countries than in high income countries, although in absolute terms the picture is reversed. Medicines to treat chronic disease are taking a larger proportion of total volume in the non-hospital sector. Projections indicate that chronic disease medicine volumes will need to increase dramatically if access is to be provided to those who need these medicines. Furthermore, usage of medicines included on the WHO Model List of essential medicines, at about 25-35%, is comparable across countries of all income categories. The results also show that there is considerable variation in the share of Original and Licensed brand products both within and across product categories and countries as compared with Other Brands and Unbranded Products. This variation may represent an opportunity for policy interventions to encourage a shift in consumption to the generally cheaper unbranded categories of products. Finally, analysis of consumption is complicated by the diversity of databases and classification systems among various countries, and within single countries due to the existence of a public and private sector. Whilst the different systems within a country can be viewed as being complementary, consumption patterns, and the impact of pharmaceutical policy in aggregate, could be clearer if data from the public and private sectors were combined. The need for more comprehensive information is particularly acute in low income countries.

**Chapter 3** contains five multi-country studies that explore possible factors of cross-national variation in medicines use in EU member states. These studies show that variation in medicines use is driven by a multitude of factors that may vary among countries and therapeutic areas. The aim of **Chapter 3.1** is to identify and assess, in terms of policy implications, the methodological problems one encounters when collecting national usage data on biologicals in a sample of different European countries, using the TNFalpha inhibitors infliximab, etanercept and adalimumab as an example. Six European countries are included in this study

providing a balanced sample in terms of heterogeneity of health-care and pharmacy systems, reimbursement rules and availability of usage data. These countries include Denmark, Finland, Ireland, the Netherlands, Norway and Portugal. Data are collected on characteristics of the nature of TNFalpha inhibitors usage data and on usage of TNFalpha inhibitors itself (2003–2007). As measured in DDDs/1000 inhabitants/day we observed an increase in TNFalpha inhibitors usage over time in all countries that varied widely from 0.32 (Portugal) to 1.89 (Norway) (2007). The results show that characteristics of TNFalpha inhibitors (usage settings and ways of distribution to patients) and databases (type of data collected, public availability and data sources) determine the type of research and policy questions that can validly be addressed. The prevailing differences in the structure of national databases are prohibitive for critical aspects of medicines utilisation studies. Finally, this study shows that in the European countries, data on national TNFalpha inhibitors usage are not easily, if at all accessible. Inter-country collaboration and sharing of technical resources will facilitate harmonization of data collection allowing independent, population based, health and outcomes research.

We further explore the use of the same medicines as a measure of access to treatment with new (expensive) medicines in **Chapter 3.2** by assessing the relationship between several components of a pharmaceutical care system and the level of medicines use. We included data from four European countries: Ireland, the Netherlands, Norway and Portugal. In 2009 we furthermore interviewed a key leading rheumatologist from each participating country to comment on the differences seen in utilisation according to the cultural context and clinical attitude towards TNFalpha inhibitors. The results show that a major driver for the utilisation of TNFalpha inhibitors seems to be the country's total health expenditure. When the use of TNFalpha inhibitors becomes more established, the association seems stronger. Differences in health expenditure are nevertheless not the only determinant of usage. Cultural aspects such as difference in recognition of guidelines also come into play when looking at differences in TNFalpha inhibitors utilisation between countries. The prospects of patients receiving TNFalpha inhibitor treatment depend on the country where they are living. In case uniformity of management and treatment would be considered to provide health benefits, the extent and the causes of variation should feature prominently on future public health agendas. **Chapter 3.3** and **3.4** focus on another class of medicines, newly approved medicines acting on the central nervous system, namely aripiprazol, duloxetine HCl and pregabalin. Comparative studies on the use of 'older' psychotropic medicines show substantial differences between European countries. A widely used argument is that attitudes and beliefs towards psychotropics differ across countries. So far, no studies look into the effects of cultural diversity on the use of new psychotropics entering the market. In **Chapter 3.3** we examine the relation between cultural diversity and utilisation of these new medicines in Europe. We calculated correlations between country level sales data up to three years after market authorization (MA) and country-specific scores of cultural dimensions. Sales data in this study were obtained through IMS Health's MIDAS database and country-specific scores of cultural dimensions were obtained from Hofstede (Power Distance, Individualism, Masculinity, Uncertainty Avoidance, Indulgence and Long-Term Orientation). Data were available for 23 European countries. We found significant

positive correlations between Indulgence and total use of the case study medicines at  $t=2$  years ( $\rho=0.51$ ,  $p=0.014$ ) and  $t=3$  years ( $\rho=0.54$ ,  $p=0.008$ ). A more detailed analysis shows (slight) variation by molecule. No correlations are found for the other dimensions. This study clearly is a first step in including cultural dimensions when explaining cross-national variation in the use of new medicines. A country's culture seems an important factor and should be considered when performing studies on cross-national variation in medicines use. However, more sustained methods need to be developed in order to compare the level of medicines use between countries, taking the cultural diversity into account. Similarly, already existing methods should be validated, such as the suitability of Hofstede's model in explaining cross-national variation in (new) medicines use.

**Chapter 3.4** concentrates on variation in the duration and outcome of national reimbursement decisions and their implications for patient access to these medicines in Europe. Our study was supported by 5 years consumption data (January 2004 – December 2009) covering 19 EU countries. Information on national reimbursement decisions was obtained through questionnaires distributed among members of the European network for Health Technology Assessment (EUnetHTA). We calculated the time from market authorization to the reimbursement decision for each country and molecule. Scatterplots were constructed to visualize the distribution of the countries according to the level of medicines use (5 years after market authorization) and the time to the reimbursement decision. The results show that consumption of the case study medicines was seen in all countries, except for duloxetine HCl in one country. The level of medicines use (5 years after market authorization) ranged from 13.1–102.0 DDDs/1000inhabitants/year for aripiprazol and from 0.0–401.6 DDDs/1000inhabitants/year for duloxetine HCl. The use of pregabalin had a range of 0.66–465.9 DDDs/1000inhabitants/year. All medicines received a positive reimbursement decision on a national level in 17 of the 19 countries. Median time from market authorization to reimbursement ranged from 6.3–14.9 months for aripiprazol, from 9.5–18.4 months for duloxetine HCl and from 6.9–20.8 months for pregabalin. There is a weak to moderate relation between the level of use (5 years after market authorization) and the time to reimbursement decision. Therefore, we concluded that when explaining causes of cross-national variation in medicines use, the effects of the (speed of) reimbursement decision should be taken into account. Finally, in **Chapter 3.5** we focus on the possible consequences of differences in the availability and uptake of new medicines for pharmaceutical care systems, in particular the contributions of EU member states to the EU regulatory network. In this analysis, we follow the uptake of all new medicines centrally approved in 2004 in the subsequent 5 years (2004–2009). Data used for this study were obtained for all 25 EU member states (per 01/05/2004), except for the Mediterranean islands of Malta and Cyprus. The results show that actual availability of these medicines vary between the individual EU countries, which is possibly a strong factor behind variation in the uptake of these new medicines. In some countries like Portugal and the Baltic States over 40% of the studied products were not available at all, even 5 years after the moment of a formal EU market authorization. The discrepancy in the uptake of medicines between EU member states seems to reflect to a certain degree the economic situation and resource

possibilities of these countries. When crossing the level of uptake of new medicines against the number of contributions to the regulatory system, defined as taking the lead in a Centralized Procedure as a (co-)rapporteur between 2004 and 2009, we found wide variability between EU member states. When this variability in contributions to the pharmaceutical regulatory system goes hand in hand with variability of actual prescribing and usage, as reflected by some countries, there is ample reason for concern about sustainability of the regulatory network that depends heavily on European partnership and community responsibility.

It remains difficult to compare some issues on medicines use, such as the effect of a specific policy measure, in various countries when no similar, preferably identical, measure regarding the same medicines and same restrictions exist in these countries. Therefore, these issues are better studied in a single country. Furthermore, patient level data are often required as these data can provide an answer to specific questions that remain unanswered when using aggregated data. **Chapter 4** concentrates on a specific example of a reimbursement restriction on benzodiazepine use in the Netherlands. Benzodiazepines were excluded as of January 2009 from the Dutch reimbursement list when used as anxiolytic, hypnotic or sedative to limit misuse and save costs. In **Chapter 4.1** we study the impact of this restriction in patients with a new diagnosis of a sleeping or anxiety disorder in general practice. We used the electronic health records-based Netherlands Primary Care Research Database to derive data on diagnoses and prescriptions. We selected patients aged 18 years and older with an incident diagnosis of sleeping disturbance or anxiety between January 2008 and December 2009. Incidence of these diagnoses, benzodiazepine use, and initiation of selective serotonin reuptake inhibitor (SSRI) treatment – as a potential unwarranted effect of the policy measure – were compared between 2008 and 2009. In total, we identified 13,596 patients with an incident diagnosis of anxiety or sleeping disorder. The proportion of patients being prescribed a benzodiazepine after a diagnosis was lower in 2009 than in 2008 for both anxiety (30.1% vs 33.7%  $P<.05$ ) and sleeping disorder (59.1% vs 67.0%,  $P<.05$ ), as was the proportion of patients with more than 1 benzodiazepine prescription for both anxiety (36.4% vs 42.6%,  $P<.05$ ) and sleeping disorder (35.0% vs 42.6%,  $P<.05$ ). We found no increase in the use of an alternative treatment for anxiety with SSRIs. Based on these findings we conclude that the reimbursement restriction has led to a moderate decrease in the number of incident diagnoses and initiation of benzodiazepine use in patients with newly diagnosed anxiety or sleeping disorder. This finding indicates that in settings where no such reimbursement opportunities exist, physicians have room to reduce benzodiazepine prescribing.

The aim of the study presented in **Chapter 4.2** was to assess patient satisfaction with the information about this reimbursement restriction. In addition, patient opinions on the reimbursement restriction and their experiences after this policy measure had taken place are examined. Thirteen community pharmacies recruited benzodiazepine users who received a questionnaire containing items on socio-demographic and health factors, satisfaction of the information services, opinions on and experiences after the policy measure. We performed logistic regression analysis including age, sex and education level to explore the association between these variables and the measured satisfaction. Overall, 372 patients were interviewed, of whom 111 (29.8%) were informed by the media only and 69 (18.6%) by health

care professionals only. Respondents informed through their health care professional were more satisfied than those informed by the media (91.3% vs. 73.9%,  $p < 0.05$ ). Younger age (<45 years) was associated with lower satisfaction of the quality of information received (adjusted OR 3.7, 95% CI:1.8-7.4). Sex, age and level of education were not associated with the attitude towards the policy measure. This analysis concludes by stating that health care professionals play an important role in distributing high quality information to patients on reimbursement changes and that their information is highly appreciated by patients. Nevertheless the majority of patients participating in this study received their information through the media. Careful attention must therefore be paid to the way patients are informed, and interventions must be tailored to the target professionals before implementing a new policy.

In the general discussion in **Chapter 5** we present the current landscape of medicines utilisation studies, discuss the key findings of this thesis on either a global, European or national level, and focus on the methodological issues raised by and encountered in the studies in this thesis. We conclude with the identification of two critical factors for performing a successful study on the extent and causes of cross-national variation in medicines use from a pharmaceutical perspective.

The first important actions for future research are to improve data harmonization and combine data(sources). By comparing and combining datasets, researchers may detect more subtle and complex associations among variables, which in the end may improve the interpretation of variation caused by historical and societal developments—the contextual environment. Furthermore, more advanced analysis techniques may need to be used to allow for the estimation of the effects of both the national or institutional context in one analysis. For better harmonization of data, close collaboration between regulatory authorities, pharmaceutical industry, research associations and academia is necessary, since the required data are often collected in large databases that are owned by single institutes.

Adequate information on the environmental context is crucial for a better understanding of variation in medicines use, and the second identified important action for future research. It is essential to hypothesize why certain pharmaceutical system factors may influence medicines use, and by which mechanism(s). Much can be learned from (methods in) international comparative studies in other research areas, such as sociological and economic studies.

To summarise, the objective outcomes of medicines utilisation studies can play a key role in helping to understand, interpret, evaluate and improve the prescription, administration and responsible use of medicines. Many key stakeholders find that these studies are valuable since the results are used to foster a more efficient use of the limited health care resources. In addition, dissemination of the outcomes of these types of studies among the general population may lead to a better understanding of the existence of restrictions on access to or availability of medicines in one's own country. The studies in this thesis show that the currently available databases and epidemiological methods provide ample opportunities for studying cross-national variation in medicines use from a pharmaceutical system perspective. However, much work remains to be done, especially in data harmonization and understanding the full pharmaceutical context.







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# CHAPTER 6.2

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NEDERLANDSE SAMENVATTING



## SAMENVATTING

Toegang tot effectieve en betaalbare geneesmiddelen wordt beschouwd als een recht voor alle Europese burgers. Het garanderen van toegang tot medische zorg, inclusief geneesmiddelen, is dan ook een uitdaging voor menig gezondheidssysteem. Gezondheidssystemen, met als onderdeel daarvan de farmaceutische systemen, vloeien voort uit politieke, historische, culturele en sociaal-economische tradities. Daarom verschillen de organisatorische regelingen voor gezondheidszorg sterk tussen de lidstaten van de Europese Unie (EU) en kunnen beleidsmakers/ambtenaren verschillende keuzes maken om de toegang tot geneesmiddelen voor hun bevolking te garanderen. Artsen verschillen in de keuzes die zij maken in de behandeling van patiënten en patiënten zelf maken verschillende keuzes in het wel of niet zoeken naar een bepaalde behandeling. Variatie in de mate en snelheid waarmee geneesmiddelen op de markt komen en de omvang van geneesmiddelengebruik tussen EU lidstaten is daarvan een vanzelfsprekend gevolg. Dit proefschrift heeft tot doel inzicht te krijgen in de variatie in geneesmiddelengebruik tussen landen. Hiertoe is het geneesmiddelengebruik bij verschillende medische aandoeningen en tussen verschillende landen bestudeerd. Bovendien zijn verscheidene kenmerken van het farmaceutische systeem gepresenteerd die mogelijk een verklaring kunnen geven voor variatie in geneesmiddelengebruik tussen landen. De uitkomsten van deze studies kunnen van meerwaarde zijn voor iedereen die zich bezig houdt met (het bevorderen van) de toegankelijkheid van geneesmiddelen.

In de inleiding (**hoofdstuk 1**) beschrijven we de hierboven genoemde variatie in geneesmiddelengebruik in verschillende landen, zoals die in eerdere studies is aangetoond. Individuele oorzaken voor verschillen in geneesmiddelengebruik zijn vaak moeilijk te identificeren, omdat een verscheidenheid aan elementen, zoals culturele of organisatorische aspecten, een specifieke rol spelen. Daarnaast kunnen factoren die bepalend zijn voor de omvang van het gebruik van een bepaald geneesmiddel anders zijn bij een ander geneesmiddel. Ook kan de variatie in geneesmiddelengebruik tussen landen verschillen per geneesmiddel. De meeste studies waren tot nu toe gericht op het in kaart brengen van de (mate van) variatie in geneesmiddelengebruik tussen landen en minder op de oorzaken voor deze verschillen. Slechts enkele studies richtten zich op de variatie in factoren die inherent zijn aan het zorgsysteem, zoals farmaceutische beleidsmaatregelen. In het afgelopen decennium is de interesse voor het bestuderen van variatie in geneesmiddelengebruik op een geïntegreerde wijze, met inbegrip van relevante kenmerken van het farmaceutische systeem, toegenomen. De studies in dit proefschrift dragen hieraan bij en laten geaggregeerde gegevens van belangrijke kenmerken van nationale farmaceutische systemen zien, vergezeld van gegevens over het feitelijke gebruik van geneesmiddelen in meerdere landen op mondiaal, Europees of nationaal niveau. De bevindingen in dit proefschrift zijn onder te verdelen in drie groepen: a) een mondiaal overzicht van nationaal geneesmiddelenbeleid en geneesmiddelengebruik, b) het verklaren van verschillen in geneesmiddelengebruik tussen Europese landen en c) het analyseren van het effect van een specifieke beleidsmaatregel op een bepaald geneesmiddel in Nederland. Als zodanig heeft dit proefschrift tot doel om richting te geven aan toekomstig onderzoek naar de

omvang en oorzaken van variatie in geneesmiddelengebruik tussen landen. Uiteindelijk zal dit moeten leiden tot betere inzichten en beleid in deze belangrijke sector in de gezondheidszorg.

In **hoofdstuk 2** presenteren we een mondiaal overzicht van variatie in nationaal geneesmiddelenbeleid en farmaceutische consumptie. **Hoofdstuk 2.1** bevat een historisch mondiaal overzicht van het ontwikkelingsproces van een *National Medicines Policy* (NMP) binnen verschillende gezondheidssystemen in de afgelopen 25 jaar. Een NMP is een document waarin het nationale geneesmiddelenbeleid op hoofdlijnen integraal wordt neergezet. Dit document wordt idealiter opgesteld door een samenwerking van belanghebbenden zoals o.a. de overheid, zorgverleners, patiënten, zorgverzekeraars, en de academie. Alhoewel de inhoud van een NMP kan variëren tussen landen is het uiteindelijk doel van elke NMP om geneesmiddelen toegankelijk te maken voor patiënten en de gezondheidszorg betaalbaar te houden. De studie toont een toename van het aantal NMPs in de wereld. Hierbij is de grootste stijging de afgelopen jaren te zien in landen met een hoog inkomen. Echter, niet alle landen hebben een NMP. Vaak is de politieke druk van nationale deskundigen of niet-gouvernementele organisaties nodig om een allesomvattend document als een NMP te genereren. Dit hoofdstuk bevat verder vier voorbeelden van de totstandkoming van een NMP. Zij laten zien dat een door de politiek gecreëerde kans, zoals bijvoorbeeld verkiezingen, meestal doorslaggevend is bij de hervorming van een NMP. Bovendien tonen deze voorbeelden aan dat het proces van totstandkoming minstens even belangrijk is als het uiteindelijke document. Het proces zorgt voor een samenkomst van belanghebbenden, hetgeen voor een gevoel van collectief eigendom van het definitieve beleid zorgt. Dit kan met het oog op de uitdagingen om een NMP te implementeren en te monitoren van cruciaal belang zijn.

**Hoofdstuk 2.2** onderzoekt de wereldwijde geneesmiddelenconsumptie binnen de ambulante sector. Gebruikspatronen in 84 landen in alle inkomenscategorieën en een verscheidenheid aan gezondheidssystemen worden beschreven. Uit de resultaten blijkt dat de consumptie in alle inkomenscategorieën is gegroeid. Het groeipercentage is groter in landen met een laag inkomen dan in landen met een hoog inkomen, hoewel dit beeld in absolute termen omgekeerd is. Geneesmiddelen ter behandeling van chronische aandoeningen hebben een groter aandeel in het totale volume dan geneesmiddelen voor acute aandoeningen in de ambulante sector. Voorspeld wordt dat het gebruik van medicatie voor chronische aandoeningen dramatisch zal toenemen als deze daadwerkelijk verstrekt gaan worden aan diegenen die deze geneesmiddelen nodig hebben. Het gebruik van geneesmiddelen die zijn opgenomen op de WHO Model Lijst van essentiële geneesmiddelen is vergelijkbaar in landen van alle inkomenscategorieën en beslaat ongeveer 25-35% van het gebruik. Uit de resultaten blijkt ook dat er aanzienlijke verschillen bestaan in het aandeel van (gepatenteerde) merkmiddelen van het totale volume tussen landen. Deze variatie betekent een kans voor beleidsmaatregelen ter bevordering van een verschuiving van de consumptie naar de over het algemeen goedkopere generieke middelen. De analyse van consumptie wordt bemoeilijkt door de diversiteit van de databases en classificatiesystemen tussen verschillende landen enerzijds, en binnen landen als gevolg van het bestaan van een publieke en private sector anderzijds. Terwijl de verschillende systemen binnen een land complementair kunnen zijn,

zouden consumptiepatronen en het effect van het farmaceutische beleid duidelijker zijn als de gegevens uit de openbare en de particuliere sector worden samengevoegd.

**Hoofdstuk 3** omvat vijf studies die mogelijke factoren van variatie in geneesmiddelengebruik in verschillende lidstaten van de Europese Unie onderzoeken. Deze studies tonen aan dat variatie in geneesmiddelengebruik wordt gedreven door een veelheid van factoren die tussen landen en therapeutische gebieden kan variëren. Het doel van **hoofdstuk 3.1** is het identificeren en beoordelen van de methodologische problemen bij het verzamelen van gegevens van het nationaal gebruik van biofarmaceutica in termen van gevolgen voor beleidsmaatregelen en onderzoek. Als voorbeeld is gekozen voor de TNFalfa-remmers infliximab, etanercept en adalimumab. Zes Europese landen zijn opgenomen in deze studie, namelijk Denemarken, Finland, Ierland, Nederland, Noorwegen en Portugal. Deze landen vormen een groep met verschillende farmaceutische systemen, vergoedingsregels en beschikbaarheid van gebruiksgegevens. In deze studie wordt gekeken naar de beschikbare informatie omtrent het gebruik van deze geneesmiddelen. Verder wordt ook de mate van gebruik (2003-2007) vergeleken. De uitkomsten tonen allereerst een toename in het gebruik aan in alle landen. Het gebruik varieert in 2007 van 0.32 (Portugal) tot 1.89 (Noorwegen) Defined Daily Dose (DDDs)/1000 inwoners/dag. Uit de resultaten blijkt verder dat karakteristieken van deze middelen (de specifieke setting waarin deze middelen worden gebruikt en de manieren van distributie onder patiënten) van invloed zijn op het type onderzoek en beleidsvragen bepalen die kunnen worden gedaan en uitgevoerd. Ook gaat invloed uit van de databases waarin de gebruiksgegevens zijn opgenomen (type van gegevens die zijn verzameld, openbare beschikbaarheid en gegevensbronnen). De verschillen in de structuur van nationale databanken bemoeilijken studies naar variatie in geneesmiddelengebruik. Daarnaast blijken nationale gebruiksgegevens van TNFalfa-remmers niet gemakkelijk toegankelijk te zijn, als ze überhaupt al beschikbaar zijn. Samenwerking tussen landen en het delen van technische middelen kan harmonisatie van gegevens faciliteren, waardoor studies, zoals uitgevoerd in hoofdstuk 3.1, vergemakkelijkt kunnen worden.

In **hoofdstuk 3.2** is verder gekeken naar het gebruik van TNFalfa-remmers. Hierbij is gekeken naar de mate van gebruik in relatie tot verschillende kenmerken van het farmaceutisch systeem. Vier Europese landen zijn bestudeerd: Ierland, Nederland, Noorwegen en Portugal. In al deze landen is een reumatoloog (opinieleider) van elk geïnccludeerd land geïnterviewd, om te reageren op de gevonden verschillen in gebruik van deze middelen vanuit een klinisch en cultureel perspectief. Uit deze studie blijkt dat de totale gezondheidsuitgaven van het land bepalend zijn voor het gebruik van TNFalfa-remmers, met name als deze middelen al enige tijd op de markt zijn. Verschillen in gezondheidsuitgaven zijn echter niet de enige factor die een rol speelt. Culturele aspecten, zoals erkenning van behandelrichtlijnen, spelen ook een rol in de verklaring voor de gevonden variatie in gebruik tussen landen. Hiermee wordt duidelijk dat de kans dat patiënten behandeld worden met één van deze middelen afhankelijk is van het land waarin zij wonen. Wanneer er in Europa gestreefd wordt naar uniforme behandeling van patiënten, dan moeten de oorzaken van de variatie in gebruik een prominentere plek krijgen op toekomstige agenda's van onderzoek naar de volksgezondheid. **Hoofdstuk 3.3** en **3.4** richten zich op een andere klasse van geneesmiddelen, de recent goedgekeurde geneesmiddelen

die werken op het centraal zenuwstelsel, namelijk aripiprazol, duloxetine HCl en pregabaline. Studies die het gebruik van 'oudere' psychotrope geneesmiddelen vergelijken, laten aanzienlijke verschillen tussen Europese landen zien. Een veel gebruikte verklaring hiervoor is dat de houding ten opzichte van en overtuigingen met betrekking tot deze middelen tussen de landen verschillen. Tot nu toe is er nog geen onderzoek gedaan waarin gekeken werd naar de effecten van dergelijke culturele verschillen op het gebruik van nieuwe psychofarmaca. In **hoofdstuk 3.3** onderzoeken we de relatie tussen culturele diversiteit en het gebruik van deze nieuwe middelen in Europa. Correlaties zijn berekend tussen verkoopgegevens van deze middelen (tot drie jaar na marktintroductie) en zes culturele dimensies. De verkoopgegevens zijn verkregen van IMS Health uit hun MIDAS database. De land-specifieke scores voor de culturele dimensies zijn verkregen via Hofstede's model (*Power Distance*, *Individualism*, *Masculinity*, *Uncertainty Avoidance*, *Indulgence* en *Long-Term Orientation*). Deze gegevens zijn voor 23 Europese landen beschikbaar. Positieve correlaties zijn gevonden tussen *Indulgence* en het gebruik van de drie middelen na 2 jaar ( $\rho = 0.51$ ,  $p = 0.014$ ) en na 3 jaar ( $\rho = 0.54$ ,  $p = 0.008$ ); hierbij is er sprake van een kleine variatie tussen de drie bestudeerde geneesmiddelen. Onder *Indulgence* wordt verstaan de mate waarin de minder machtige leden van instituties of organisaties in een land verwachten en accepteren dat de macht ongelijk verdeeld is. Is deze verwachting en acceptatie laag, dan spreekt men van een kleine machtsafstand. Voor de andere dimensies zijn geen correlaties gevonden. Deze studie is duidelijk een eerste stap naar meer inzicht in de rol van culturele dimensies bij het verklaren van variatie in het gebruik van nieuwe geneesmiddelen tussen landen. De cultuur van een land lijkt een belangrijke factor en moet worden meegenomen bij toekomstige studies naar variatie in geneesmiddelengebruik tussen landen. Echter, betere methoden moeten worden ontwikkeld om de culturele diversiteit te meten in de context van geneesmiddelengebruik. Hiertoe moet ook de geschiktheid van reeds bestaande methoden worden bekeken, zoals Hofstede's model voor het verklaren van variatie in het gebruik van (nieuwe) geneesmiddelen tussen landen.

**Hoofdstuk 3.4** concentreert zich op de variatie in de duur en de uitkomsten van nationale vergoedingsbesluiten en de gevolgen daarvan voor het gebruik van aripiprazol, duloxetine HCl en pregabaline. De studie omvat 19 EU landen en kijkt naar gebruik van deze middelen over een periode van 5 jaar (januari 2004 – december 2009). Informatie over nationale vergoedingsbesluiten is verkregen via vragenlijsten verspreid onder leden van het Europees netwerk voor Health Technology Assessment (EUnetHTA). Centraal in de analyse stond de tijd tussen de toelating tot de markt en het vergoedingsbesluit voor elk land en elk van de drie geneesmiddelen in dit onderzoek. Gekeken is of de spreiding tussen landen in het gebruik van de bestudeerde middelen (tot 5 jaar na de handelsvergunning) samenhangt met de tijd die het kost in een land om tot een vergoedingsbesluit te komen. Uit de resultaten blijkt dat alle drie de bestudeerde geneesmiddelen in alle landen worden gebruikt, met uitzondering van duloxetine HCl in Polen. De omvang van het geneesmiddelengebruik (5 jaar na de handelsvergunning) is 13.1–102.0 DDDs/1000inwoners/jaar voor aripiprazol, 0.0–401.6 DDDs/1000inwoners/jaar voor duloxetine HCl en 0.66–465.9 DDDs/1000inwoners/jaar voor pregabaline. In 17 van de 19 landen is er een positief vergoedingsbesluit gevallen voor alle drie de middelen.

De gemiddelde tijd van toelating tot de markt tot vergoeding varieert van 6.3–14.9 maanden voor aripiprazol, van 9.5–18.4 maanden voor duloxetine HCl en van 6.9–20.8 maanden voor pregabalin. De samenhang tussen de omvang van het gebruik (5 jaar na verkrijging van de handelsvergunning) en de tijd die het kost tot een vergoedingsbesluit genomen is, is matig tot zwak. De resultaten tonen aan dat, weliswaar in geringe mate, het verkorten van de tijd tot een vergoedingsbesluit, effect kan hebben op de omvang van het gebruik op een langere termijn (5 jaar na verkrijging van de handelsvergunning). In **hoofdstuk 3.5** bekijken we naar de relatie de rol van EU lidstaten aan het regulatoire netwerk en de beschikbaarheid en niveau van gebruik van nieuwe geneesmiddelen. In deze analyse volgen we de opname van alle in 2004 centraal goedgekeurde geneesmiddelen in de daaropvolgende vijf jaar (2004-2009). Gegevens voor deze studie zijn verkregen voor 25 EU-lidstaten (per 01/05/2004), met uitzondering van de mediterrane eilanden Malta en Cyprus. De resultaten tonen variatie aan in de werkelijke beschikbaarheid van deze geneesmiddelen tussen de afzonderlijke EU landen, hetgeen mogelijk een sterke factor is achter de variatie in adoptie van deze nieuwe geneesmiddelen. In sommige landen zoals Portugal en de Baltische Staten is meer dan 40% van de onderzochte producten geheel niet beschikbaar, zelfs niet 5 jaar nadat de formele EU handelsvergunning is afgegeven. De discrepantie in de opname van geneesmiddelen tussen EU lidstaten lijkt tot op zekere hoogte de economische situatie van deze landen te reflecteren. Landen verschillen sterk in de mate waarin zij bijdragen aan het systeem van regelgeving; dit is in deze studie gedefinieerd als het voortouw nemen in een gecentraliseerde procedure als (co-)rapporteur in de centrale procedure tot markttoelating. Kijken we naar de relatie tussen deze bijdragen en de omvang van het geneesmiddelen gebruik tussen 2004 en 2009, dan kunnen we drie groepen van landen identificeren. Landen die een hoge bijdrage hebben aan het regulatoire netwerk en een hoog niveau van geneesmiddelengebruik, landen die gemiddeld tot laag bijdragen aan het regulatoire netwerk maar toch een hoog niveau van geneesmiddelengebruik hebben en landen die nauwelijks bijdragen aan het regulatoire netwerk en een laag niveau van geneesmiddelengebruik hebben. De gevonden variaties zijn op zich niet nieuw, maar als de variabiliteit in bijdragen aan de farmaceutische regelgeving hand in hand gaat met de variabiliteit van het daadwerkelijk voorschrijven en gebruik, zoals weerspiegeld door sommige landen, dan is er alle reden tot bezorgdheid over de duurzaamheid van het regulatoire netwerk. Dat is namelijk sterk afhankelijk van Europees partnerschap en gezamenlijke verantwoordelijkheid.

Het blijft moeilijk om sommige kwesties inzake geneesmiddelengebruik te vergelijken tussen verschillende landen. Dit geldt bijvoorbeeld voor het effect van beleidsmaatregelen, die niet in andere landen genomen zijn. Dergelijke kwesties kunnen dan ook beter worden bestudeerd in een enkel land. Bovendien blijven sommige specifieke vragen onbeantwoord bij het gebruik van geaggregeerde gegevens omdat dan vaak gegevens vereist zijn op patiëntniveau. **Hoofdstuk 4** concentreert zich op de beperking van de vergoeding van benzodiazepinegebruik in Nederland. Benzodiazepinen, wanneer gebruikt als anxiolyticum, hypnoticum of kalmerend middel, zijn per januari 2009 van de Nederlandse vergoedingslijst geschrapt om misbruik te beperken en kosten te besparen. In **hoofdstuk 4.1** bestuderen we de invloed van deze beperking op patiënten met een nieuwe diagnose van een slaap- of

angststoornis in de huisartspraktijk. Dit gebeurt met de elektronische medische dossiers van de NIVEL zorgregistraties met daarin opgenomen gegevens over diagnoses en voorschriften. De studie heeft betrekking op patiënten van 18 jaar en ouder met een nieuwe diagnose slaapstoornis of angststoornis tussen januari 2008 en december 2009. De incidentie van deze diagnoses, benzodiazepinegebruik en start van een behandeling met selectieve serotonine heropname remmer (SSRI) - als een mogelijk ongerechtvaardigd gevolg van de beleidsmaatregel - zijn vergeleken tussen 2008 en 2009. In totaal betreft de studie 13.596 patiënten met een nieuwe diagnose van een angst- of slaapstoornis. Het aantal patiënten dat een benzodiazepine krijgt voorgeschreven na vaststelling van deze diagnose is lager in 2009 dan in 2008, zowel bij angst- (30,1% vs. 33,7%  $P < .05$ ) als bij slaapstoornissen (59,1% vs. 67,0%,  $P < .05$ ). Ook het aantal patiënten met meer dan één benzodiazepinerecept voor zowel angst (36,4% vs. 42,6%,  $P < .05$ ) als een slaapstoornis (35,0% vs. 42,6%,  $P < .05$ ) is lager. Er is geen toename in het gebruik van een alternatieve behandeling van angst met SSRIs. Op basis van deze bevindingen kunnen we concluderen dat de beperking van de vergoeding heeft geleid tot een lichte daling van het aantal nieuwe diagnoses en van een daling van initiëren van benzodiazepinegebruik bij patiënten met een recent gediagnosticeerde angst- of slaapstoornis. Deze bevinding geeft aan dat artsen ruimte hebben om minder benzodiazepines voor te schrijven indien geen vergoedingsrestricties bestaan.

Het doel van de studie in **hoofdstuk 4.2** is om tevredenheid van patiënten over de informatie rondom deze vergoedingsbeperking te beoordelen. Benzodiazepinegebruikers in dertien openbare apotheken vulden een vragenlijst in met vragen over socio-demografische en gezondheidsfactoren, de manier van en de tevredenheid over de verkregen informatie en meningen over en ervaringen na de beleidsmaatregel. Driehonderd twee en zeventig patiënten zijn geïnterviewd, van wie 111 (29,8%) alleen door de media werden geïnformeerd en 69 (18,6%) alleen door professionals in de gezondheidszorg. Logistische regressie analyses met bovengenoemde factoren aangevuld met de factoren leeftijd, geslacht en onderwijsniveau tonen aan dat patiënten die op de hoogte waren gesteld via hun zorgverlener meer tevreden waren dan zij die op de hoogte waren gebracht door de media (91,3% versus 73,9%,  $p < 0,05$ ). Jongeren ( $< 45$  jaar) zijn minder tevreden over de kwaliteit van de ontvangen informatie dan mensen van 45 jaar en ouder (gecorrigeerde odds ratio (OR) van 3.7, 95% CI:1.8-7.4). Geslacht, leeftijd en opleidingsniveau hangen niet samen met de houding ten opzichte van de beleidsmaatregel. Deze analyse laat zien dat professionals in de gezondheidszorg een belangrijke rol spelen bij het verspreiden van kwaliteitsinformatie over vergoedingswijzigingen aan patiënten en dat hun informatie wordt gewaardeerd door patiënten. Toch ontving de meerderheid van de patiënten die deelnamen aan deze studie hun informatie via de media. Aandacht moet daarom worden besteed aan de manier waarop patiënten worden geïnformeerd, en interventies moeten worden afgestemd op de doelgroep van professionals vóór de implementatie van een nieuwe beleidsmaatregel.

In de algemene discussie gepresenteerd in **hoofdstuk 5** beschrijven we het huidige landschap omtrent studies naar het gebruik van geneesmiddelen. Verder bediscussiëren we de belangrijkste bevindingen van dit proefschrift op drie niveaus (mondiaal, Europees en nationaal) en richten we ons op de methodologische kwesties die voorkwamen in de studies in



dit proefschrift. De discussie wordt afgesloten met de identificatie van twee kritische factoren die van belang zijn bij het uitvoeren van studies naar de omvang en oorzaken van variatie in geneesmiddelgebruik tussen landen vanuit een farmaceutisch perspectief.

De eerste belangrijkste actie voor toekomstig onderzoek is het verbeteren van de harmonisatie van gegevens, alsmede het combineren van gegevens en gegevensbronnen. Door het vergelijken en/of het combineren van datasets kunnen onderzoekers subtielere en complexere associaties ontdekken tussen verschillende variabelen. Deze associaties kunnen uiteindelijk leiden tot een verbetering van de interpretatie van variatie veroorzaakt door historische en maatschappelijke ontwikkelingen, of te wel de contextuele omgeving. Bovendien zullen meer geavanceerde analysetechnieken moeten worden gebruikt om in één enkele analyse een schatting te kunnen maken van de effecten van zowel de nationale als de institutionele context. Aangezien de vereiste data vaak worden verzameld in (grote) databases die beheerd worden door individuele instituten, is voor een betere harmonisatie van gegevens een nauwere samenwerking noodzakelijk tussen regelgevende instanties, farmaceutische industrie, onderzoeksinstituten en de wetenschap.

De tweede geïdentificeerde kritische factor voor toekomstig onderzoek is het beschikken over adequate informatie over het gehele systeem. Daarbij is het van essentieel belang dat van te voren wordt nagedacht welke kenmerken van het farmaceutische systeem geneesmiddelengebruik kunnen beïnvloeden en wat de onderliggende mechanisme(n) zijn. Hierbij kan veel geleerd worden van methodes zoals die gebruikt worden in internationaal vergelijkend onderzoek in andere onderzoeksgebieden, zoals sociologische of economische studies.

Samenvattend kan gesteld worden dat de resultaten van onderzoek naar het gebruik van geneesmiddelen een sleutelrol kunnen spelen in het begrijpen, interpreteren, evalueren en verbeteren van het voorschrijven, de toediening en het verantwoord gebruik van geneesmiddelen. Veel betrokkenen vinden de uitkomsten van zulke studies waardevol. Immers, de uitkomsten kunnen bijdragen aan een efficiënter gebruik van de schaarse middelen in de gezondheidszorg. Bovendien kan het verspreiden van de onderzoeksresultaten onder de algemene populatie leiden tot een beter begrip van genomen maatregelen rond geneesmiddelen, zoals de afschaffing van een vergoeding voor een bepaald geneesmiddel.

De studies in dit proefschrift tonen aan dat de huidige databases en epidemiologisch methodes ruime mogelijkheden bieden voor studies naar variatie in geneesmiddelengebruik tussen landen vanuit een farmaceutisch perspectief. Echter, nog veel werk dient te worden verricht, vooral in de harmonisatie van gegevens en het begrijpen van informatie omtrent de farmaceutische context.



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# CHAPTER 7

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ADDENDUM



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# CHAPTER 7.1

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DANKWOORD



Wat een goed gevoel, om de studies waar je zoveel energie en enthousiasme in hebt gestopt, gebundeld te zien in een heus proefschrift. Echter, zoals prof. dr. Hubert Leufkens het al verwoordde op één van de eerste dagen dat ik met mijn promotie begon: 'niet het einddoel is het belangrijkste, maar de weg ernaar toe'. Op dat moment kon ik me daar nog geen goed beeld van vormen. Nu weet ik, promoveren is als een ontdekkingsreis; spannend, inspannend, leerzaam en leuk! Hij had het dus niet treffender kunnen zeggen. Er valt zo ontzettend veel te zien, leren en ontdekken. In het begin weet je nog niet goed waar het eindpunt ligt en welke wegen je moet bewandelen om er te komen. Soms ga je de verkeerde kant op, maar weet je daardoor des te beter hoe verder te gaan en andere keren ontdek je op onverwachte momenten hele mooie dingen. Ik vond het heel leuk! Dit alles was echter niet mogelijk geweest zonder de bijdrage van vele personen die ik dan ook heel hartelijk wil bedanken.

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# CHAPTER 7.2

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# CHAPTER 7.3

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LIST OF PUBLICATIONS



### Scientific publications included in this thesis

Hoebert JM, Mantel-Teeuwisse AK, van Dijk L, Laing RO, Leufkens HGM.

Quality and completeness of utilisation data on biological agents across European countries:

Tumour Necrosis Factor alpha inhibitors as a case study

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National Medicines Policies – A review of the evolution and development processes

Conditionally approved for publication in South Med Rev

Hoebert JM, Laing RO, Stephens P.

Global Pharmaceutical Consumption

In: World Health Organization, World Medicines Situation Report 2011, Geneva, 2013 (3rd Edition)

Hoebert JM, Mantel-Teeuwisse AK, Leufkens HGM, van Dijk L.

Variability in market uptake of psychotropic medicines in Europe reflects cultural diversity

Submitted for publication

Hoebert JM, Kleijnen S, van Dijk L, Leufkens HGM, Mantel-Teeuwisse AK.

Waiting for reimbursement? – Patient access to three new psychotropic medicines in Europe

Submitted for publication

Hoebert JM, van Geffen ECG, van Dijk L, Mantel-Teeuwisse AK, Philbert D, Bouvy M.

Reimbursement restriction on benzodiazepines: information services for patients and their experiences

Submitted for publication

### Scientific publications not included in this thesis

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Benzodiazepinegebruik daalt als de gebruiker zelf betaalt.

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National Medicines Policies

In: World Health Organization, World Medicines Situation Report 2011, Geneva 2013 (3rd Edition)





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# CHAPTER 7.4

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ABOUT THE AUTHOR





Joëlle Martine Hoebert was born on the 30<sup>st</sup> of October 1981 in Utrecht, the Netherlands. Most of her early youth she spend abroad, in Indonesia and Portugal (1982-1991). Back in the Netherlands, she finished her secondary school (gymnasium) in 1999 at the Scholengemeenschap 'Pantarijn' in Wageningen. Thereafter, she started her studies in Pharmacy at Utrecht University. As part of her study she completed a research internship at the Centre for Pharmacoepidemiological Research of the National Association of Pharmacies in Lisbon, Portugal. During her studies she was an accomplished field hockey player at S.V. Kampong (Utrecht), and has won several national and one world title indoor hockey. In 2006 she obtained her Master's degree in Pharmacy, followed by her Pharmacist's degree (PharmD) in 2008. Between July 2008 and December 2012, she worked full time on the studies described in this thesis as a PhD student at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences, Faculty of Science of Utrecht University under the supervision of Prof. dr. Bert Leufkens and Dr. Aukje Mantel-Teeuwisse. She worked in close collaboration with Dr.ir. Liset van Dijk from NIVEL, the Netherlands Institute for Health Services Research and Prof. dr. Richard Laing from the Department of Essential Medicines and Pharmaceutical Policies, World Health Organization (WHO). During this period Joëlle obtained a Master's degree in Epidemiology at the Graduate School of Life Sciences, Utrecht University. As of July 2013 she works as a scientist at the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. Joëlle is married to Jos Hoes and they have a daughter Sofia (2011) and a son Daan (2012).

