This product is part of the RAND Corporation technical report series. Reports may include research findings on a specific topic that is limited in scope; present discussions of the methodology employed in research; provide literature reviews, survey instruments, modeling exercises, guidelines for practitioners and research professionals, and supporting documentation; or deliver preliminary findings. All RAND reports undergo rigorous peer review to ensure that they meet high standards for research quality and objectivity.

TECHNICAL REPORT

International variation in the usage of medicines

A review of the literature

Ellen Nolte, Jennifer Newbould, Annalijn Conklin

Prepared for the Department of Health within the PRP project "An 'On-call' facility for International Healthcare Comparisons"

RAND EUROPE

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

The research described in this report was prepared for the Department of Health within the PRP project "An 'On-call' Facility for International Healthcare Comparisons" (grant no. 0510002).

Published 2010 by the RAND Corporation
1776 Main Street, P.O. Box 2138, Santa Monica, CA 90407-2138
1200 South Hayes Street, Arlington, VA 22202-5050
4570 Fifth Avenue, Suite 600, Pittsburgh, PA 15213-2665
Westbrook Centre, Milton Road, Cambridge CB4 1YG, United Kingdom
RAND URL: http://www.rand.org
RAND Europe URL: http://www.rand.org/randeurope
To order RAND documents or to obtain additional information, contact
Distribution Services: Telephone: (310) 451-7002;
Fax: (310) 451-6915; Email: order@rand.org

Preface

This report reviews the published and grey literature on international variation in the use of medicines, focusing on osteoporosis, atypical anti-psychotics, dementia, rheumatoid arthritis, cardiovascular disease/lipid-regulating drugs (statins), and hepatitis C. The report aims to inform the Steering Group "Extent and Causes of International Variation in Drug Usage" to guide further analytical work on the extent and causes of international variation in drug usage.

The report was prepared as part of the project "An 'On-call' Facility for International Healthcare Comparisons" funded by the Department of Health in England through its Policy Research Programme (grant no. 0510002). The project comprises a programme of work on international health care comparisons that provides intelligence on new developments in other countries, involving a network of experts in a range of OECD countries to inform health policy development in England. It is conducted by RAND Europe, in conjunction with the London School of Hygiene & Tropical Medicine.

RAND Europe is an independent not-for-profit research organisation whose mission is to improve policy and decision making through research and analysis. RAND Europe's clients include European governments, institutions, NGOs, and firms with a need for rigorous, independent, multidisciplinary analysis.

The London School of Hygiene & Tropical Medicine is Britain's national school of public health and a leading postgraduate institute worldwide for research and postgraduate education in global health.

For more information about this report, please contact:

Dr Ellen Nolte
Director, Health and Healthcare
RAND Europe
Westbrook Centre, Milton Road
Cambridge CB4 1YG

Email: enolte@rand.org
Tel: +44 (0)1223 273853

Contents

Tables

Executive summary

In July 2009 the Department of Health established a Steering Group "Extent and Causes of International Variation in Drug Usage" to guide analytical work to better understand the extent and causes of international variation in drug usage. This report aims to contribute to this process by reviewing the published and grey literature on international variation in the use of medicines in six areas (osteoporosis, atypical anti-psychotics, dementia, rheumatoid arthritis, cardiovascular disease/lipid-regulating drugs (statins), and hepatitis C).

The systematic search found surprisingly few international comparative studies that examined medicines use and these varied widely in terms of quality and focus, populations and time periods studied, and outcomes measured. However, despite this variation several common issues emerged from the evidence reviewed here. We identify three broad groups of determinants of international variation in medicines use:

- Macro- or system level factors. Differences in reimbursement policies, and the role of health technology assessment, were highlighted as a likely driving force of international variation in almost all areas of medicines use reviewed here, including dementia, rheumatoid arthritis, hepatitis C, and, for some countries in central and eastern Europe, statins. A related but rarely studied aspect is patient co-payment, potentially explaining some of the international variation in medicines use, which is likely to play an important role in the United States in particular, compared with European countries; but the extent to which cost-sharing policies impact on overall use of medicines in international comparison remains unclear.
- Service organisation and delivery. Most studies reviewed here pointed to differences in access to specialists as a likely driver of international variation in areas such as atypical anti-psychotics, dementia, and rheumatic arthritis, with for example access to and availability of relevant specialists identified as acting as a crucial bottleneck for accessing treatment for dementia and rheumatoid arthritis.
- Clinical practice. Several studies highlighted the role of variation in the use and ascertainment methods for mental disorders, and differences in the use of clinical or practice guidelines. Many studies further pointed to differences in prescribing patterns as an important factor, along with a potential reluctance among clinicians in some countries to take up newer medicines, but none of the studies presented here provided empirical evidence to support this notion.

Each of these factors is likely to play a role in explaining international variation in medicines use, but their relative importance will vary depending on the disease area in question and the system context. It is likely that any given level of use of a given medicine in one country is determined by

a set of factors the combination and the relative weight of which will be different in another country.

Acknowledgements

The project "An 'On-call' Facility for International Healthcare Comparisons" is funded by the Department of Health in England through its Policy Research Programme (grant no. 0510002).

The authors gratefully acknowledge the valuable comments provided by Martin Roland and Jonathan Grant on an earlier draft of this report.

The views expressed in this report brief are those of the authors alone and do not necessarily represent those of the Department of Health. The authors are fully responsible for any errors.

CHAPTER 1 Background

The 2008 review *Improving Access to Medicines for NHS Patients* highlighted that there is a perception among stakeholders that usage of new medicines is low in England when compared with other countries, especially for new anti-cancer drugs.[1] However, building on preliminary analyses of international data on usage of medicines for the treatment of selected disease areas including cancer, the review pointed to the considerable (technical) challenges related to comparing international medicines usage and that the extent, causes and implications of such variations are not fully understood. One of the recommendations set out by the review therefore highlighted the need to examine international variation in medicines usage more systematically so as to inform future policy decisions on funding for drugs.[1] Subsequent to the review the Department of Health established a Steering Group "Extent and Causes of International Variation in Drug Usage" to guide further analytical work on the extent and causes of international variation in drug usage, which began in the context of the 2008 review. This report aims to contribute to this process by reviewing the published and grey literature on international variation in the use of medicines in selected areas.

This report focuses on six (disease) areas: (1) osteoporosis, (2) atypical anti-psychotics, (3) dementia, (4) rheumatoid arthritis, (5) cardiovascular disease/lipid-regulating drugs (statins), and (6) hepatitis C. The review is based on a systematic search of PubMed, complemented by a targeted search of websites of (inter)national organisations considered relevant to the medicine and/or condition under review, including the European Medicines Agency (EMEA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The review concentrates on evidence of international variation in medicines usage and we therefore only consider studies that explore cross-national variation involving at least two countries.

In order to capture the potentially varied literature we applied broad search terms, using combinations of ("/" indicating "or") "use/utilization/consumption/ prevalence", "therapy/treatment/medication", "international/cross-national/Europe/ America", and "variation/difference/comparison" linked to the individual medicine or medicine class (e.g. "alendronate" to represent bisphosphonates for the treatment of osteoporosis; "atypical anti-psychotics"; "statins") for the treatment of the disease/conditions and/or to the actual disease (e.g. "rheumatoid arthritis"). The search was restricted to selected new and/or high-cost medicines in each of the seven areas as identified by the Steering Group and listed in Appendix A. Appendix B provides a description of the search terms and strategies used for each area.

The search was limited to studies published from 2000 onwards. We imposed this restriction mainly because the majority of medicines reviewed here were only licensed in the 2000s. Furthermore, pharmaceutical policies that are likely to exert an influence on drug usage have

changed considerably in a number of countries during the past decade, with for example the introduction of reference pricing, parallel imports, or the use of negative/positive lists; an example is the impact of the introduction of reference pricing on the use of statins in Germany.[2 3] Studies that predate these policies are unlikely to inform a better understanding of causes of contemporary variation in medicines usage.

Titles and abstracts were screened for eligibility for inclusion. Studies considered eligible were retrieved where possible and scrutinised further for inclusion or exclusion in the review. References in studies considered eligible were followed up where appropriate. We generally excluded studies that examined the (cost-) effectiveness and/or safety of the medicines in question, clinical and drug trials, etiological (observational) studies, and those that examined patient adherence. We also excluded review articles except as a source for the identification of international comparative studies not identify by our search.

Overall the systematic search identified surprisingly few studies of international variation in the use of the medicines under review and none for osteoporosis. In the latter case we therefore also considered studies of patient preferences that, while not directly comparing usage of the listed medicines for the treatment of osteoporosis (Appendix A), provided some indirect evidence that could offer insights into the possible causes for international variation in the usage of these medicines. We included only studies comparing medicines usage in high-income/OECD countries, with a particular focus on Europe, Canada, and the United States. We thus excluded studies comparing medicines usage among the devolved countries of the United Kingdom. Studies in languages other than English, German, or French were also excluded.

Eligible studies were further analysed by extracting data according to a common template:

- stated study objective
- study design (type of study)
- year
- population/s studied
- data source
- outcome measure/s
- key findings.

Where appropriate, we included a brief commentary to highlight specifics of the study in question that are likely to influence the generalisability of the findings (e.g. data are not population based).

CHAPTER 2 Osteoporosis

The PubMed search identified 317 records of which none was considered eligible for inclusion according to the inclusion criteria set out in the preceding section. We further reviewed the websites of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, the International Osteoporosis Foundation, and the European Federation of Pharmaceutical Industries and Associations (EFPIA). This search yielded two related reports on the management of osteoporosis in the 27 Member States of the European Union in 2008.[4 5] The report focused, among other things, on access to diagnostics and treatment in each Member State, but did not analyse uptake or usage of medicines for the treatment of osteoporosis and so was not included in our review.

An earlier scanning of the literature undertaken to inform the search strategy used here identified one study that examined women's treatment preferences for osteoporosis in different countries.[6] Duarte et al. (2007) undertook a cross-sectional survey of postmenopausal women with osteoporosis in France, Germany, Mexico, Spain and the United Kingdom (n=600 in each country) to determine the relative importance of seven medication attributes in assessing participant preferences for osteoporosis medication. The importance women placed on different attributes differed among countries, with effectiveness rated as most important in their preference for a prescription osteoporosis medication ranging from 49 per cent in Mexico to 71 per cent in France. The role of out-of-pocket payments was generally rated as of low importance in France, Germany, Spain and the United Kingdom (at under 8 per cent of all women surveyed), but not Mexico (16 per cent). Among women treated for osteoporosis, alendronate was the most commonly used medication in most countries (26 per cent of all respondents), from 14 per cent in Mexico to 34 per cent in Germany.[6]

CHAPTER 3 Atypical anti-psychotics

The PubMed search identified 205 records of which seven studies met our inclusion criteria. We further searched the websites of Mind; the Prescribing Observatory for Mental Health, hosted by the Royal College of Psychiatrists (UK); the Mental Health Foundation; the Working Group Drugs in Psychiatry (AGATE); and the European Federation of Pharmaceutical Industries and Associations (EFPIA). This search did not identify any additional comparative studies that met our inclusion criteria.

Of the seven studies that included two or more countries with regard to the use of atypical anti-psychotics (AAPs), one pooled pharmacists' data on AAP use and polypharmacy in 45 hospitals in six countries (Belgium, Denmark, France, Germany, the Netherlands and Scotland).[7] It found that frequencies of atypical polypharmacy ranged between 26.1 per cent (Germany) and 49.1 per cent (Belgium) (Table 1). However, the authors noted that the study was not designed to analyse variation in the use of atypical anti-psychotics, with several countries underrepresented in their study and therefore findings have to be interpreted with caution. Santamaria et al. (2002) analysed trends in the use of anti-psychotics in Spain between 1985 and 2000 using sales data, and then compared these to published sales data in five Nordic countries (Table 1).[8] However, the comparison with the Nordic countries does not allow for conclusions about cross-national trends for consumption of AAPs specifically.

Zito et al. (2008) compared the annual prevalence in 2000 of any psychotropic medication in young people (0–19 years) in the Netherlands, Germany and the United States (Table 1).[9] They found relatively modest cross-national differences in the prevalence of total anti-psychotics (from 0.34 per 100 youth in Germany to 0.76 per 100 youth in the United States), but the proportion of AAPs in relation to total anti-psychotic use was much lower in Germany (5 per cent) than in the two comparator countries (48 per cent in the Netherlands and 66 per cent in the United States). The authors discussed a number of factors that might explain observed variations in psychotropic medication in young people in the three countries although they did not distinguish factors specifically related to AAP use. Potential explanatory factors put forward include differences in diagnostic classification between the United States (using Diagnostic and Statistical Manual (DSM) criteria) and European countries (application of the International Classification of Diseases version 10); higher prevalence of concomitant use of two or more medications in the United States; and access to specialists such as child psychiatrists, which tended to be lower in European countries; however, the authors did not provide empirical evidence in support of this discussion.[9]

Four studies analysed cross-national variation in AAP use among selected, psychiatric (in)patient populations in different countries, usually focusing on prescription patterns. Thus, Hübner-

Liebermann et al. (2005) compared inpatient treatment of patients with schizophrenia in two hospitals in Germany and Japan, using data from the psychiatric basic documentation system in 1997.[10] The rate of usage of AAPs was 18 per cent at the German hospital and 12 per cent at the Japanese hospital (Table 1). Potential explanations for the observed variation put forward by the authors include differences in service provision and national psychiatric practices. The authors also commented on availability and affordability as a possible cause for country variation since AAPs in 1997 were rare in Japan as elsewhere in the Asian region, except for zotepine. However, as their study only compared single hospitals in each country, the findings are not easily generalisable.

Zullino et al. (2005) analysed psychotropic drug prescriptions, including of AAPs, in five German and Swiss psychiatric hospitals (with a total of 572 patients) in 1999.[11] Although the proportion of patients receiving antidepressants varied significantly between the two countries, with a higher propensity among Swiss clinicians than clinicians at the three German hospitals to prescribe psychotropic drugs (at 65.2 per cent compared with 48.3 per cent), AAP prescriptions did not vary between Germany and Switzerland. However, a higher proportion of patients in Germany received clozapine (at 70.8 per cent of prescribed AAP) than in Switzerland (43.9 per cent). In discussing their findings, the authors largely focused on potential explanations for the observed variation in antidepressants, including differences in the patient population, hospital-specific factors, and cost considerations. There was little discussion of the observed lack of such a variation in AAP prescribing although the higher proportion of prescribing clozapine in German hospitals might point to possible lack of uptake of newer medicines in Germany. However, it is important to stress that although the five hospitals included in the study were selected to represent university and non-university settings, as well as urban and rural areas, generalisability of findings is limited.

Haro et al. (2003) analysed the baseline characteristics of patients recruited into the Schizophrenia Outpatient Health Outcomes (SOHO) study in ten western European countries in 2000 and 2001 (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain and United Kingdom).[12] Atypical anti-psychotic treatment in the six months prior to recruitment to the study varied between countries, from a high of 60.6 per cent in Denmark and 58.1 per cent in Portugal to a low of 34.2 per cent in Germany and 27.4 per cent in Greece. There was considerable variation in the use of specific AAPs at baseline, with usage rates (defined as receiving an AAP) of risperidone of 9.1 per cent in Ireland; around 13 per cent in Germany and Portugal; 16 per cent in the United Kingdom; 18 per cent Denmark and Italy; 22 per cent in France, the Netherlands and Spain; and 30.7 per cent in Greece. Use of amisulpride varied from 16 per cent in Ireland; to 10 per cent in France; to no use in Denmark, the Netherlands, Greece or Spain, where the drug was not available at that time (2001/02). The use of clozapine ranged from a high of 12.1 per cent in Denmark; to between 5 per cent and 6 per cent in Ireland, the United Kingdom and Italy; 3.6 per cent in the Netherlands; 2.7 per cent in Germany; 1–2 per cent in Portugal, Spain and Greece; and 0.5 per cent in France. The authors noted that these variations are not likely to reflect differences in sociodemographic or clinical patient characteristics, but represent treatment differences across countries, listing local prescribing practices, availability of treatment guidelines, and cost as potential variables that

might explain observed differences in patterns of use. However, their study was not designed to explore variation in treatment patterns.

Finally, Bitter et al. (2003) reported on the findings of a multi-centre comparative study of prescribing practices for acute inpatients with schizophrenia (429 patients) in six academic psychiatric departments in China, Japan, Hungary, and the United States in 1999.[13] There was considerable variation between centres regarding the proportion of patients receiving AAPs, ranging from a high of 73–75 per cent in one Hungarian centre (Budapest 1) and China (Shanghai) to a low of just under 9 per cent in the Japanese centre (Tokyo) (Table 1). However, these differences were not statistically significant when adjusted for differences in demographic variables. The authors highlighted several limitations of their study, including representativeness of the patients, prescribers and hospitals, so findings are not easily generalisable.

Although these four studies provide important insights into possible international variation in usage of AAPs, the representativeness of findings is somewhat limited given the design of each study, involving only single or a low number of medical units in the relevant countries under review and/or the study was not set up to explore variation in AAP use.

Table 1 Summary of studies of international variation in the use of atypical anti-psychotics (AAPs)

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To investigate the extent of simultaneous prescribing of atypical anti-psychotics, conventional anti-psychotics and anticholinergics in daily clinical practice	Pharmacoepidemio-logical study of pharmacists in 45 hospitals in Belgium, Denmark, France, Germany, the Netherlands, and Scotland	11/1998 – 10/1999	Prescription data	2,725 patients using AAPs for more than six weeks	Frequencies of simultaneous prescription of atypical anti-psychotics with other anti-psychotics and/or anticholinergics	Gives range of frequencies of atypical polypharmacy only: between 26.1% (Germany) and 49.1% (Belgium); without low-potent APs they vary between 17.1% (Denmark) and 31.6% (Belgium)	Study not designed to detect differences in AAP use in different countries (some countries underrepresented)	[7]
(1) To analyse the trend of anti-psychotic drug consumption in Spain, comparing it with that of Nordic countries (2) To evaluate the impact of the introduction of newer AAPs	Pharmacoepidemio-logical study of national drug consumption	1985–2000	Retail community pharmacy sales as recorded in Spanish Ministry of Health database National sales data for Nordic countries	Populations of Spain and of five Nordic countries as comparator	DDD/1,000/d	2000: 5.73 (all anti-psychotic drugs) 1.31 (risperidone) 1.21 (olanzapine) ~0.1 (clozapine) 0 (sertindole, quetiapine) (Data on AAP use in Nordic countries not reported)	Data on trends do not include hospital use and so might underestimate trends in consumption over time and across countries	[8]
To compare the prevalence of psychotropic medication use in youth	Cross-sectional population-based analysis of administrative claims data in three countries	2000	Administrative claims data	Insured outpatient youth aged 0–19 in the Netherlands, Germany, and the USA	Annual prevalence of use defined as the dispensing of one or more prescriptions for a psychotropic drug per 100 enrolled youth	% AAP to total anti-psychotic use was 5% in Germany, 48% in the Netherlands, and 66% in the USA	US data based on one state only so generalisability of findings may be limited; lack of diagnostic data does not allow inference about indication of prescribed medicines	[9]
To evaluate facets of psychiatric inpatient care of patients in a German and a Japanese hospital	Pharmacoepidemio-logical study of patients with schizophrenia admitted to two hospitals each in a different country	1997	Psychiatric basic documentation system	865 German inpatients and 50 Japanese inpatients with schizophrenia	Frequencies of psycho-pharmacological treatment	The rate of AAP use was 18% in Germany (clozapine) and 12% in Japan (zotepine)	Unit of analysis: single hospitals in two countries limiting the generalisability of findings	[10]

Table 1 Summary of studies of international variation in the use of atypical anti-psychotics (AAPs) - *continued*

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To compare drug prescriptions between German and Swiss psychiatric services with regard to their preference of newer psychotropics	Pharmacoepidemio-logical study of psychiatric inpatients in five hospitals in Germany (n=3) and Switzerland (n=2)	1999	Administrative data on drug prescriptions	572 psychiatric inpatients	Proportion of patients receiving psychotropic drugs including AAPs (clozapine, olanzapine, risperidone, and amisulpride)	Proportion of patients receiving AAP varied between 25% and 45% but this variation was not significant and did not differ by country; proportion of patients receiving clozapine was higher in German hospitals (at 70.8% of prescribed AAP compared with 43.9% in Swiss hospitals)	Data were adjusted by age and sex; although the five hospitals were selected to represent university and non-university settings as well as urban and rural areas, generalisability of findings is limited	[11]
To describe the baseline findings and study population of the Schizophrenia Outpatient Health Outcomes (SOHO) Study	Three-year prospective, observational study of the health outcomes associated with anti-psychotic treatment in ten European countries (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	Recruit ment: 9/2000–12/2001	Core data collection form (DCF); data collected by participating psychiatrists (n=1096)	10,972 out-patients with schizophrenia who initiate therapy or change to a new anti-psychotic	Anti-psychotic medication along with a wide range of demographic, clinical, and social indicators	Atypical anti-psychotic treatment in the six months prior to inclusion in the study varied between countries: Denmark (60.6%), Portugal (58.1%), Ireland (43.6%), the UK (42.9%), Spain (40.7%), France (401.%), the Netherlands (39.2%), Italy (38.5%), Germany (34.2%), and Greece (27.4%); average: 37.6%	Analyses baseline characteristics of population recruited into the study; study not designed to analyse variation in AAP use	[12]
To compare prescription practices for acute inpatients with schizophrenia among six academic departments in four countries	Pharmacoepidemio-logical study of psychiatric inpatients in six academic departments in China (Hong Kong; Shanghai), Japan (Tokyo), Hungary (Budapest; n=2), and the USA (New York)	1999	Standardised data collection form	429 inpatients with clinical diagnosis of schizophrenia	Number and dose of AP, AAP and depot APs; other psychotropic drugs; and multiple APs	Proportion of patients receiving AAP was highest in one Budapest centre: 73.1% and Shanghai: 74.6%; Hong Kong: 38%; Budapest 2: 36%; New York: 42.7%; Tokyo: 8.9%	Unit of analysis: single hospitals in four countries limiting the generalisability of findings	[13]

CHAPTER 4 Dementia

The PubMed search yielded 217 records, of which two met the inclusion criteria. In addition we searched the websites of the following organisations: European Dementia Consensus Network, Alzheimer's Research Trust, Alzheimer Europe, the National Institute on Ageing, For Dementia, and the European Federation of Pharmaceutical Industries and Associations (EFPIA), but this search did not identify additional studies considered eligible.

Pariente et al (2008) examined the prevalence of cholinesterase inhibitor (ChI) treatment in nine European countries (Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain and the United Kingdom) in 2004 (Table 2).[14] Use of ChIs (donepezil, rivastigmine, and galantamine) in dementia patients varied greatly across countries, ranging from a low in the Netherlands (3.0 per cent), to 5.9 per cent in Italy, 6.7 per cent in the United Kingdom, 17.5 per cent in Spain and 20.3 per cent France. For those treated with a single drug, donepezil was the most frequently used ChI across all countries except the Netherlands, where this drug was not marketed at the time of the study (2004); use ranged from 47 per cent in Spain to 72 per cent in the United Kingdom. The proportion of those using rivastigmine was relatively higher in France (20 per cent), Belgium (26.4 per cent), Germany (22.5 per cent), and the United Kingdom (17.3 per cent), but very low in Poland (0.2 per cent). Galantamine was used more frequently in Spain (33.5 per cent), Portugal (24 per cent), Poland (30.4 per cent), Italy (25.7 per cent), and the Netherlands (85 per cent), but less so in the United Kingdom (10.6 per cent), Germany (14 per cent), and France (16.2 per cent).

The authors discussed a range of potential factors that might explain variation in dementia drug use, in particular the role of what they broadly term "health policies", in this instance referring to reimbursement policies. For example, countries such as the Netherlands require a complex negation process for reimbursement involving clinical, biological, and radiological information for each patient who required dementia medication. Reimbursement of national health insurance systems varied and ranged from 0 per cent in Italy to 100 per cent in the United Kingdom. As the initial prescription of ChIs is restricted to specialists such as neurologists, psychiatrists, and geriatrists, variation in usage might also be caused by availability of specialists.

Table 2 Summary of studies of international variation in the use of medicines for the treatment of dementia

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To evaluate the prevalence of cholinesterase inhibitor (ChI) treatment in subjects with dementia in European countries	Pharmacoepidemiological study of prevalence of ChI use	2004	Sales (IMS Health) and reimbursement data (donepezil, rivastigmine, and galantamine); estimates of dementia prevalence	Subjects with dementia in nine European countries (Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, and UK)	Prevalence of treatment in subjects with dementia	Prevalence of treatment with ChIs varied: Netherlands (3.0%), Italy (5.9%), the UK and Germany (6.7%), Poland (7.9%), Portugal (11.2%), Belgium (13.8%), Spain (17.5%), and France (20.3%)	Potential limitations of findings: (1) rely on ecological data for the prevalence of dementia and drug utilisation; (2) noted inconsistencies of IMS data in relation to dosage estimates	[14]
To examine access to ChIs across the European Union	Cross-sectional survey of clinical experts in 23 countries	2005	Survey of accessibility of four dementia drugs (rivastigmine, galantamine, donepezil, and memantine)	One clinical expert in each of 23 countries(Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxemburg, Malta, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the UK)	(1) drug is licensed (yes/no) (2) drug is reimbursed (fully/partial/no) (3) GPs are allowed to initiate (yes/no) and continue treatment (yes/no)	Variability in accessibility of drug treatment across EU. Only six countries (Switzerland, Ireland, Sweden, Malta, Germany, and Luxemburg) allowed GPs to initiate dementia treatments. Variability in reimbursement: 12 of the 23 countries provided full reimbursement for all four of the drugs studied; variation in restrictions posed on reimbursement from none (e.g. Ireland and Switzerland) to various (the Netherlands)	Survey includes one expert per country who had to meet certain requirements (clinical duties in patient care for people with dementia; authored at least one publication regarding dementia in a peer-reviewed journal in 2004 or 2005); representativeness of findings might be questionable	[15]

For example, the authors argued that the "relative lack" of relevant specialists in the United Kingdom could partly explain the low rates of ChI use in the country, despite the full reimbursement of treatment costs for patients.

However, Pariente et al. (2008) stressed that although health policies constitute an important determinant of observed differences, they do not explain all variations in ChI usage. Other factors to be taken into account include variation in diagnosis of dementia, and the authors pointed to the introduction of a plan of action for Alzheimer's disease in France in 2001, which aimed at improving dementia detection and treatment and which is likely to have increased the number of people diagnosed with the disease and, consequently, the number of patients receiving treatment, although data to confirm this hypothesis could not be presented. Other potential reasons include differences in prescribing patterns among European countries (although not specific to dementia drugs), citing evidence that the more than 70 per cent of medical consultations tend to result in a prescription in countries such as France and Germany while occurring in less than half of consultations in the Netherlands, for example.[14]

Oude Voshaar et al. (2006) examined the accessibility of donepezil, rivastigmine, memantine, and galantamine for patients with dementia across Europe by surveying clinical experts in 23 European countries in 2005 (Table 2).[15] "Clinical expert" was defined as a clinician who (1) had to have clinical duties in patient care for people with dementia and (2) had authored at least one publication on dementia in a peer-reviewed journal in 2004 or 2005. Other than galantamine in Hungary and donepezil in the Netherlands, all of the medicines under review had been licensed throughout the EU. However, countries varied with regard to the indications for which dementia medicines were licensed. For example, memantine was licensed for mild to moderate Alzheimer's disease in Slovenia, Slovakia, and Malta only, but it was licensed for moderate to severe Alzheimer's disease in all the other countries included in the survey.

Oude Voshaar et al. (2006) demonstrated that countries varied greatly with regard to the role of the GP in initiating dementia treatment, which was only authorised in six countries (Switzerland, Ireland, Sweden, Malta, Germany, and Luxemburg), while eight countries prohibited GPs from continuing anti-dementia drug treatment initiated by specialists (Netherlands, Belgium, France, Slovakia, Czech Republic, Austria, Hungary, and Portugal).[15] Reimbursement rates also varied across countries. Only 12 of the 23 countries studied provided full reimbursement for all four of the medications studied, with the remainder providing only partial reimbursement. Galantamine was not reimbursed in four countries (Hungary, Lithuania, Malta, and Poland), memantine in three countries (Hungary, Malta, and Poland), rivastigmine in two countries (Lithuania and Malta), and donepezil in two countries (Malta and the Netherlands). In addition, countries differed in the restrictions they imposed on reimbursement, with some imposing no restrictions (e.g. Ireland and Switzerland), while others based reimbursement decisions on treatment protocols for Alzheimer's disease (e.g. the Netherlands and Belgium). Several countries also required permission from the relevant funder prior to treatment (Netherlands, France, Luxembourg, and Denmark). In addition, in the Netherlands, although memantine was licensed for moderate to severe dementia, it was only reimbursed for severe dementia.

This study provides important insights into the possible causes of variation in dementia drug use across European studies. For example, the findings for the Netherlands in relation to restrictions imposed on reimbursement might explain, in part, the low use of ChIs in that country; France also required prior approval yet the use of dementia medicines was relatively high (Table 2). It should however be emphasised that the survey of clinical experts was undertaken in 2005 and it is likely that countries' policies on treatment pathways and accessibility of drugs under the statutory system has changed since.

CHAPTER 5 Rheumatoid arthritis

The PubMed search identified 955 titles of which four studies met the inclusion criteria. The websites of the following organisations were searched for grey literature: Arthritis Care, the National Rheumatoid Arthritis Society, Arthritis Research Campaign, Rheumatology Information Service Europe, and the European Federation of Pharmaceutical Industries and Associations (EFPIA), the latter identifying one additional document.[16] Of the four studies identified, Sokka et al. (2007) presented the findings of a cross-sectional review of the treatment of unselected consecutive outpatients with rheumatoid arthritis in 15 countries.[17] However, although this study analysed the use of disease-modifying antirheumatic drugs (DMARDs) it did not disaggregate for the new biological drugs (TNF inhibitors) of interest here and we therefore did not include this study in our review.

Jönsson et al. (2008) examined international variation in use of TNF inhibitors (etanercept, infliximab, and adalimumab) and of conventional DMARDs (aurothiomalic acid, auranofin, and leflunomide) (Table 3).[18] The study examined the period 2000 to 2006 in 30 countries and showed that the United States had the fastest and most extensive uptake of TNF drugs as measured by sales data. By the end of 2006, the US rate was in excess of €350,000 per 100,000 population (data are presented as graphs only with exact figures not reported), approximately three times the average in western European countries and Canada. High uptake was also observed for Norway (~€350,000/100,000), Sweden (~€300,000/100,000), the Netherlands (~€250,000/100,000), and Finland (~€200,000/100,000). France, Spain, and the United Kingdom were approximately at the E-13 average (defined as EU-15 countries excluding Portugal, Ireland, Greece, and Luxemburg, but with the addition of Norway and Switzerland), at around €130,000 per 100,000 population, while Germany (~€110,000/100,000) and particularly Italy (~€70,000/100,000) were below average, as was Australia (~€20,000/100,000). Indeed, the level of uptake seen in Australia was more akin to the levels observed for the ten countries of central and eastern Europe that were also included in the study, at an average level of €10,000/100,000. Within the (western) European market, and after correcting for differences in the prevalence between northern and southern Europe, by the end of 2006, France and Spain had the highest uptake, at around €550 per patient with rheumatoid arthritis (RA); uptake was lower in the United Kingdom (~€400/patient with RA), Germany (~€350/patient), and Italy (~€300/patient) (E-13 average: ~€400/patient).

The estimated number of patients per 100,000 population treated with TNF inhibitors was highest in the United States (around 140 per 100,000 population) and Norway

(~120/100,000). The lowest rates were seen in Australia, Slovenia, and the Czech Republic at around or under 10/100,000.

When disaggregated by individual TNF inhibitor, the relative "ranking" of countries changed somewhat, with for example the United Kingdom well above the E-13 average for the use of etanercept (~€120/patient with RA compared with E-13 average at €90/patient) but lower for infliximab (~€45/patient compared with €60/patient) and, in particular, adalimumab (~€30/patient compared with €60/patient). In contrast, Germany was shown to be well below the E-13 average (and the United Kingdom) for the use of etanercept (~€80/patient) and infliximab (~30/patient) but well above for the use of adalimumab (~70/patient).

In trying to explain observed variations in the uptake of TNF inhibitors, Jönsson et al. (2008) noted differences in national income (as measured by GDP) as a possible reason for the much lower use of these medicines in the countries of central and eastern Europe compared with western Europe, Canada, and the United States.[18] However, at the same time there were also considerable differences between countries with broadly the same GDP. Relative price levels might explain some of the variation, with, for example, the relatively high price in Germany believed to have affected access. Yet, although there were substantial differences in prices for TNF inhibitors, high and low use was not systematically related to differences in price.

The authors highlighted the possible role of health technology assessment (HTA) in uptake, noting that countries with a strong HTA tradition, combined with a societal perspective, tended to show greater uptake of TNF inhibitors such as Sweden and Norway compared with countries that tend to apply stricter health care cost approaches such as the United Kingdom and Australia, and so concluding that international variation in the uptake of these medicines reflects national preferences and priorities.[18] However, the authors emphasised that the nature of the data examined did not allow for establishing a clear cause–effect relationship of this hypothesised association. They further pointed to a potential role of variations in access to specialists (rheumatologists), with an estimated density of 1/25,000 population in France and 1/50,000 in the United States, compared with only 1/150,000 in the United Kingdom and 1/200,000 in Germany, which might explain some of the observed variations in uptake between countries.

Table 3 Summary of studies of international variation in the use of medicines for the treatment of rheumatoid arthritis (RA)

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To compare uptake of RA treatment across countries	Pharmaco-epidemiological study of uptake of TNF inhibitor in 30 countries	2000–2006	Commercial databases (IMS Health) (etamercept, infliximab, and adalimumab)	Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Romania, Russia, Slovak Republic, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, the UK, and the USA	Total sales (in €) per 100,000 population for class and individual TNF inhibitor; "crude" rate and adjusted for disease prevalence; estimated number of patients receiving TNF inhibitor treatment	Estimated number of patients per 100,000 population treated with TNF inhibitor was highest in USA (~140 per 100,000 population) and Norway (~120/100,000); followed by Sweden and Netherlands (~75–80); Denmark, Belgium, Finland, and Luxembourg (~60); Canada (~50); UK and Switzerland (~40); Spain, France, and Italy (~35); Germany (~25); Austria (<20); Australia, Slovenia, Czech Republic, and Slovakia (<10)	Study does not report exact figures; all data are presented as graphs	[18]
To present new data and expand the discussion on issues on access, costs, and value created by biological treatments (of RA)	Pharmaco-epidemiological study of uptake of biological treatments of RA in 30 European countries	4th quarter 2008	Commercial databases (IMS Health) (etamercept, infliximab, adalimumab, anakinra, rituximab, and abatacept)	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the UK	Total sales (in €) per 100,000 population; estimated number of patients receiving biological treatment for RA; estimated drug quantity per prevalent patient; proportion of prevalent patients on treatment	Norway had the highest proportion of RA patients on biological treatment (~30%); followed by Belgium and Ireland (20%); Denmark, Luxembourg, Spain, Greece, Switzerland, Finland, France, and the Netherlands (>10–<20%); UK (10%); Germany, Italy, and Portugal (>5–<10%); Slovenia, Czech Republic, Austria, Hungary, Slovakia, Estonia, Lithuania, Latvia, Romania, Poland, and Bulgaria (5% and less)	Study does not report exact figures; all data are presented as graphs	[16]
To analyse associations between clinical status of RA and GDP of patients resident country	Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) cohort	Since 2005	QUEST-RA, clinical and questionnaire data	6,004 patients seen in usual care in 25 countries (4/2008) (Argentina, Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, the Netherlands, Poland, Russia, Serbia, Spain, Sweden, Turkey, the UK, United Arab Emirates, and the USA)	DMARD medication incl. proportion of patients ever receiving biological agents; country's GDP	Proportion of patients ever having received biological agents varied widely: 53–54% (France and Greece); 42% (Ireland); 33% (Sweden and USA); 25–29% (Germany, Italy, Spain, and Brazil); 23% (Denmark and Netherlands); 20% (UK); 15–19% (Finland, Hungary, and Russia); 10–14% (Lithuania, UAE, and Poland); <10 (Turkey); <5% (Estonia, Kosovo, Serbia, and Argentina)	Primary study focus on RA disease activity rather than medicines use; also findings based on limited number of patients in each country	[19]

Building on the work by Jönsson et al. (2008),[18] Kobelt and Kasteng (2009)[16] examined the uptake of biologic treatments of rheumatoid arthritis in 30 European countries (27 EU Member States plus Iceland, Norway, and Switzerland) in the fourth quarter of 2008 (Table 3). The study used sales data and estimates of the prevalence of rheumatoid arthritis, and found Norway to have the highest proportion of RA patients receiving treatment with biological drugs (at just under 30 per cent) by the end of 2008. High proportions of patients receiving biological treatment for RA were also seen in Belgium and Ireland (at around 20 per cent), followed by Denmark, Luxembourg, and Spain (~17 per cent), while proportions were lower in the United Kingdom (at 10 per cent), Germany (8 per cent), and in particular Austria (<5 per cent), compared with an E-13 average of about 11 per cent.

Annual sales per patient broadly mirrored these figures. The only exceptions were Germany where the higher manufacturer price of biological RA medicines resulted in higher sales per patient close to the E-13 average (at ~€1250/patient with RA) despite a low proportion of patients on treatment, and the United Kingdom where mg usage and proportion of patients on treatment were close to the E-13 average, but sales per patient fell well below the E-13 average (at ~€900/patient) as a consequence of currency fluctuations (depreciation of Pound Sterling relative to the Euro).

In addition to the reasons for variation in usage of biological treatments already noted by Jönsson et al. (2008)[18], such as national income and relative price levels, Kobelt and Kasteng (2009) also pointed to the role of clinical guidelines.[16] For example, eligibility of patients for biological treatment of RA varies among countries with those requiring a higher disease activity score tending to have a lower use of these drugs, such as in Italy and the United Kingdom. Importantly, however, the authors highlighted that there is not one single explanation for the differences in uptake of biological treatments in the different countries in Europe. Although a number of economic, organisational, and clinical factors play a role, the relative impact of each is likely to differ among systems.

Sokka et al. (2009) (Table 3) examined data from the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) project, involving clinical and questionnaire data from 6,004 patients seen in usual care at 70 rheumatology clinics in 25 (18 European) countries by April 2008.[19] Among other things, the study analysed the use of disease-modifying antirheumatic drugs (DMARDs), including the proportion of patients who ever had received biological agents. This proportion varied widely among countries, from a high in just under 55 per cent in France and Greece and 42 per cent in Ireland down to less than 5 per cent in Estonia, Kosovo, Serbia, Turkey, and Argentina (Table 3). The United Kingdom tended to be at the lower end of the spectrum, at 20 per cent, as did Denmark and the Netherlands, at 23 per cent, with Germany at 29 per cent, and Sweden and the United States at 33 per cent. These proportions are somewhat different from those estimated by Kobelt and Kasteng (2009), which found proportions of RA patients receiving biological treatment to be lower in Germany than in, for example, the United Kingdom, Spain, and Italy.[16] Clearly, the data underlying both studies are not easily comparable as those presented by Sokka et al. (2009) are based on patients with an established diagnosis of RA[19] while the figures presented by Kobelt and Kasteng (2009) are based on sales data and population-based estimates of RA prevalence.[16]

In an attempt to explain observed disparities in RA disease activity, Sokka et al. (2009) correlated clinical status of patients with RA with the GDP of the country patients resided in. This analysis demonstrated that the burden of rheumatoid arthritis was higher in countries termed "low GDP" countries (GDP capita < US$ 11,000; n=11 countries) than in "high GDP" countries (GDP/capita > US$ 25,000; n=14). Importantly, when analysing further for disease activity levels and medication, the authors showed that it appears to be disease activity levels rather than current medications that are associated with the wealth of a given country. Furthermore, the current use of biological agents appeared to have a greater inverse association with disease activity in ''low GDP'' than in ''high GDP'' countries, further underlining the authors' notion that medication is only partly associated with a given nation's wealth.

CHAPTER 6 Cardiovascular disease lipid-regulating drugs/statins

The PubMed search identified 964 records. The websites of the following organisations were searched for grey literature: Euro-Med-Stat, the British Heart Foundation, the European Heart Network, and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Ten studies met our inclusion criteria. Of these, two examined and/or compared different data sources to assess usage of medicines, both of which used statin use in European Union Members States as an example.[20 21] We have not included these two studies in the tabular review (Table 5) below but will briefly report on their findings regarding the comparability of different databases (Box 1). We were unable to retrieve one study by Goodman et al. (2009) reporting on the management of approximately 32,000 patients with acute coronary syndromes enrolled at 184 hospitals in 25 countries within the Global Registry of Acute Coronary Events (GRACE) study.[22]

Walley et al. (2004) examined statin use in 13 European countries in 2000, using national administrative databases (Table 4).[23] They found the use of statins to vary widely between countries. The prevalence of use was highest in Norway, at 59.28 DDD (defined daily doses)/1,000 inhabitants/d and lowest in Italy, at 14.74 DDD/1,000/d (Table 4). Differences in morbidity were suggested as a potential cause for observed differences in use between countries, such as that observed between Italy and the United Kingdom; however, the authors noted that this explanation did not fully account for all variance, such as that observed between Norway and Denmark, with statin use in the former almost fourfold that seen in the latter (Table 4). Factors unique to specific countries might therefore explain some of the variation, such as the involvement of Norway in seminal trials while the Danish public system only introduced these medicines from 1998 onwards. Overall, the authors point to the role of political, cultural, and social factors as a cause for variation, but these factors are not elaborated further.[23]

Table 4 Use of statins in European countries in 2000

Country	Rate of use for all statins (DDD/1,000 of population covered/d)
Austria	21.94
Belgium	39.32
Denmark	15.50
Finland	30.85
France	55.82
Germany	26.47
Ireland	26.38
Italy	14.74
Netherlands	47.28
Norway	59.28
Portugal	19.06
Spain	24.13
Sweden	34.29
UK	23.86

SOURCE: [23]

In a subsequent study, Walley et al. (2005) (Table 5) examined the use of lipid-lowering drugs, primarily statins (simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin) across Europe using data from administrative and commercial databases during 1997–2003.[24] Statins were the most frequently used lipid-lowering drugs across Europe, although fibrates accounted for 25 per cent of lipid-lowering agents in France and Belgium, and 10 per cent of those used in Germany. Use of statins varied across countries; based on administrative data, in 2003 statin use was highest in Ireland and Norway, at just under 100 DDD per 1,000 inhabitants and days, and lowest in Austria and Italy, at around 30 DDD/1,000/d (data were presented in graph format only so precise figures are difficult to assess). Using Intercontinental Marketing Services (IMS) data, which were available for nine countries only, the study found a similar pattern of use, with the highest levels again seen in Ireland, at 99.29 DDD/1,000/d, and the lowest in Italy, at 37.12 DDD/1,000/d. Although the market leader varied in different countries, the most common statins used were simvastatin and atorvastatin.

It is important to note that over the study period (1997–2003) the use of statins increased considerably across all countries reviewed by Walley et al. (2005), with the median annual increase at 35.6 per cent per year, ranging between and 13.8 per cent/annum in France and 54 per cent/annum in Ireland associated with the dissemination of compelling evidence of effectiveness during this period.[24] This increase was explained by higher prescribed daily doses and increases in numbers of patient days of treatment, the latter possibly either due to more patients being treated or, less likely, improved adherence. Differences in prescribed daily doses between countries may relate to marketing differences. The authors noted that although increases in patient treatment days and prescribed daily doses might explain some variation between countries, they highlight the

need for further research to examine the roles of reimbursement regulations, morbidity, and local medical and patient culture as possible further explanations for variations in the use of lipid-lowering drugs between countries.

Box 1 Comparing medicines use in different countries

Walley et al. (2004) compared the use of national administrative and commercial IMS data to monitor expenditure and costs of statins across 11 EU countries and Norway in 2000.[21] The analysis demonstrated consistent differences in the information provided by these two sources. Thus, the commercial data tended to record greater utilisation, reflecting that IMS data record both public and private use, while administrative databases cover publicly funded services only. Also, commercial data tended to give a lower cost per defined daily doses, because these used ex-factory price rather than actual expenditure to the relevant national/regional authority paying for public services as recorded in administrative databases. However, utilisation per 1,000 population per day was similar between the two sources. The authors therefore concluded that administrative databases give useful utilisation data which are broadly comparable with those from commercial sources. However, commercial data (IMS) recorded greater utilisation than administrative sources but this varied between countries. Figures were reported to be most alike for Finland and Norway and most disparate in Ireland.

The work by Walley et al. (2004)[21] drew on administrative datasets compiled by the EURO-MED-STAT Group (2003), which aimed to develop indicators to monitor price, expenditure, and utilisation of medicinal products in the EU, so as to facilitate international comparisons.[20] Using lipid-lowering medication as an example of producing an inventory of data sources and assessing the reliability of data, the study highlighted the challenges to comparing medicines use across Europe because of variation in availability and differences in pack size, tablet strength, and manufacturer.

Also drawing on administrative databases, Cooke et al. (2005) compared two non-EU countries, examining statin use in Nova Scotia Canada and Queensland Australia.[25] Over the five-year period 1997–2001 the overall use of statins in the two regions was similar (Table 5). Statin use increased in both regions and there were no statistically significant differences in overall use, rising from 50 DDD per 1,000 beneficiaries per day in 1997 to 205 DDD/1,000/d in 2001. This is despite differences in pharmaceutical industry marketing strategies, with for example exposure to direct to consumer advertising in Canada (through availability of mass media from the United States where direct to consumer advertising is not prohibited), but not in Australia, pharmaceutical reimbursement arrangements, cost of statins (slightly higher in Canada), pharmaceutical brand availability, and prescribing policies (a restriction on prescribing of statins applied in Queensland).

Four studies examined cross-national variations in statin use among populations at risk of or with established (heart) disease. Thus, Carruthers et al. (2005) reported on findings of a multinational, prospective, observational registry (GRACE: Global Registry of Acute Coronary Events) of patients with acute coronary syndromes (ACS), comparing the

management of ACS patients in the United Kingdom with those in a set of European countries (data from Austria, Belgium, France, Germany, Italy, Poland, and Spain combined) and multinationally (data from Argentina, Australia, Brazil, Canada, the United States, and New Zealand combined).[26] The study found that in-hospital pharmacological management of ACS patients varied among regions, with statin use most frequent in the United Kingdom, at 73 per cent, compared with the European (58 per cent) and multinational populations (43 per cent). At the same time, other treatments such as with glycoprotein IIb/IIIa antagonists and ACE inhibitors were prescribed less frequently in the United Kingdom, at 6 per cent, compared with 25 per cent in the European group and 26 per cent multinationally. In explaining the variation in treatment the authors pointed to differences in clinical practice as the most likely cause.

Bhatt et al. (2006) analysed data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry on the treatment of cardiovascular risk factors in an outpatient population with atherothrombosis from 5,473 physician practices in 44 countries between 2003 and 2004.[27] Medication use varied based on geography, with statin use lowest in Japan, at 44.6 per cent, and highest in the Middle East, at 82.4 per cent. High levels of statin use were also seen in Australia (78.8 per cent) and North America (76.9 per cent), followed by Western Europe (69.9 per cent), Latin America (64.2 per cent), Asia (60.5 per cent), and Eastern Europe (57.6 per cent). The authors further demonstrated that there was also substantial variation in patients' medication use by physician specialty, with cardiologists prescribing statins significantly more often than other physician specialties, at 83.2 per cent compared with, for example, general practitioners, at 75.9 per cent. However, these data were not disaggregated by country so it is difficult to assess whether this finding holds similarly across all countries included in the survey.

More recent work by Kotseva et al. (2009) presented findings from the EUROASPIRE III survey of lifestyle, risk factors, and use of cardioprotective medicines in Europe in 2006 to 2007.[28] Data from patient interviews six months after hospital discharge following a coronary event suggested that although reported use of statins was generally high, at 78 per cent on average, it varied substantially, from 95.4 per cent in Finland to 42 per cent in Lithuania. Use was also high in countries such as Ireland, the United Kingdom, Spain, and Italy, at almost 90 per cent, followed by France, Belgium, and Germany at around 85–87 per cent. However, it is important to note that data are based on a population of patients from selected geographical areas and usually academic hospitals; thus usage data are not necessarily representative for all people with coronary heart disease in a given country.

Using the same EUROASPIRE III dataset, Cooney et al. (2009) examined, among other things, statin use in Ireland, confirming that at 91 per cent usage was significantly higher than the European average (79 per cent).[29] However, similar issues on the generalisability of the findings to the Irish population apply given that the Irish arm of the EUROASPIRE III survey included two Dublin centres only.

In an attempt to explain observed variation on the use of lipid-lowering drugs among the EUROASPIRE III survey population more generally, Kotseva et al. (2009) highlighted the likely role of health care funding and reimbursement strategies, which will be relevant in a small number of countries participating in the survey.[28] However, they also noted the continued variation among western European countries, possible pointing to differences in

professional attitudes to and patient preferences for treatment, but the authors do not provide further (empirical) evidence to support this hypothesis.

Table 5 Summary of studies of international variation in the use of statins

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To assess the use of statins across Europe	Pharmaco-epidemiological study of statin use	2000	(Sub)national administrative databases	Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, and the UK (England)	Prevalence of medication use (DDD/1,000 inhabitants/d)	Use of statins across Europe was extensive but variable; use was highest in Norway (59.28 DDD/1,000/d) and lowest in Italy (14.74) (Table 4)	Administrative datasets used limited to publicly funded systems	[23]
To describe trends in utilisation and prescribing of statins and other lipid-lowering drugs across Europe	Observational study comparing annual utilisation data for lipid-lowering agents by class and drug	1997–2003	National administrative databases (13 countries); commercial databases (IMS Health) (9 countries)	12 EU members states (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, and the UK) and Norway	Prevalence of medication use (DDD/1,000 inhabitants/d)	Use of lipid-lowering drugs increased across EU during study period; in 2003, use varied (DDD/1,000/d): Belgium 74.74; England: 71.03; Finland: 66.07: France: 75.19; Germany: 45.90; Ireland: 99.29; Italy: 37.17; Netherlands: 82.90; and Spain: 48.73	Limitations of IMS data noted	[24]
To investigate the feasibility of using available prescription administrative databases to compare the use of statins in Queensland, Australia, and Nova Scotia, Canada	Pharmaco-epidemiological study of utilisation of statins for 1997–2001	1997–2001	Nova Scotia Pharmacare Program; Health Insurance Commission Australia	Beneficiaries of public drug plan in Nova Scotia, Canada; concession beneficiaries in Queensland, Australia (both populations mainly (~60%) 65 years and older)	Medication use (DDD/1,000 beneficiaries/d)	Utilisation of statin medications comparable between the two populations, at 50 DDD/1,000/d in 1997 and 205 DDD/1,000/d	Focus on two provinces/regions might limit generalisability to the entire population in each country	[25]
To determine to what extent evidence based guidelines are followed in the management of acute coronary syndromes (ACSs) in the UK, elsewhere in Europe, and multinationally, and what the outcomes are	Multinational, prospective, observational registry (GRACE, global registry of acute coronary events) involving 94 hospitals in 14 countries	1999–2000	Standardised case record form	1,511 patients with ACS in UK; 6,505 patients with ACS in Austria, Belgium, France, Germany, Italy, Poland, and Spain; 12,264 patients with ACS in Argentina, Australia, Brazil, Canada, the USA, and New Zealand	Main outcome measure: death during hospitalisation and at six months' follow up; in-hospital pharmacological treatment	In-hospital prescribing of statins was highest in the UK (73%) compared with the European (58%) and multinational groups (43%) (other treatments such as glycoprotein IIb/IIIa antagonists and ACE inhibitors were prescribed less often in the UK, at 6% compared with comparators at 25% and 26%)	Study population identified from selected geographical areas (e.g. UK cluster set in the southeast of Scotland) so limited generalisability to management of ACS patients in given country	[26]

Table 5 Summary of studies of international variation in the use of statins - *continued*

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To determine whether atherosclerosis risk factor prevalence and treatment would demonstrate comparable patterns in many countries around the world	International, prospective, observational registry of outpatients (aged 45+) with established coronary artery disease, cerebrovascular disease, peripheral arterial disease, or with at least three atherosclerosis risk factors (REACH registry)	2003–2004	Standardised international case report form, completed at the study visit	67,888 patients (aged 45+) from 5,473 physician practices in 44 countries: North America (Canada and USA); Latin America (Brazil, Chile, Mexico, and Interlatina); Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, the Netherlands, Portugal, Spain, Sweden, and the UK); Eastern Europe (Bulgaria, Hungary, Lithuania, Romania, Russia, and Ukraine); Middle East (Israel, Lebanon, Saudi Arabia, and UAE); Asia (China, Hong Kong, Indonesia, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand); Australia; Japan	Baseline prevalence of atherosclerosis risk factors, medication use, and degree of risk factor control	Medication use varied based on geography; statin use was lowest in Japan, at 44.6%, and highest in Middle East, at 82.4% (North America: 76.9%; Latin America: 64.2%; Western Europe: 69.9%; Eastern Europe: 57.6%; Asia: 60.5%; Australia: 78.8%; and Japan: 44.6%)	Study has limitations inherent to non-population-based registries – generalisability of findings to the given country is limited	[27]
To report on the principal results of EUROASPIRE III on the practice of preventive cardiology	Cross-sectional survey of patients with coronary heart disease (CHD) in 22 countries	2006–2007	Patient medical records and patient interview and examination	8,966 patients with first or recurrent diagnosis or treatment of CHD in 76 hospitals in 22 countries (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Romania, Russia, Slovenia, Spain, Turkey, and the UK)	Reported medication (cardioprotective drugs), prevalence of CHD disease risk factors; therapeutic control of blood pressure and blood sugar	Reported use of statins was generally high, at 78% on average; use varied from 95.4% in Finland to 42% in Lithuania; >90%: Cyprus, Greece, and Poland >85%: Belgium, Czech Republic, France, Ireland, Italy, Spain, and the UK; >80%: Croatia, Germany, and Romania; >70%: Hungary, Latvia, the Netherlands, and Turkey: 65%; Bulgaria: 59%	Survey population identified from selected geographical areas and mainly academic hospitals so not representative of all CHD patients in given country	[28]
To compare the Irish results of EUROASPIRE III with the rest of Europe	Cross-sectional survey of patients with coronary heart disease (CHD) in 22 countries	2006–2007	Patient medical records and patient interview and examination	386 Irish patients with first or recurrent diagnosis or treatment of CHD in two Dublin centres; non-Irish patient population of EUROASPIRE III (figure not given)	Reported medication (cardioprotective drugs), prevalence of CHD disease risk factors; therapeutic control of blood pressure and blood sugar	Use of statins was significantly higher in Ireland than in the rest of the EUROASPIRE III population, at 91% compared with 79%	Survey population identified from two centres in Dublin and so not representative of all CHD patients in Ireland	[29]

CHAPTER 7 Hepatitis C

The PubMed search identified 91 records of which one study met our inclusion criteria. We also searched the website of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Lettmeier et al. (2008) examined the market uptake of peginterferons for the treatment of hepatitis C in 21 European countries during 2000–2005.[30] The study found that peginterferon sales (per 1,000 population) varied by region, with highest sales seen among the group of EU Founding Members (Belgium, France, Germany, Italy, and the Netherlands), which were also found to be the earliest and most rapid adopters of peginterferons. These were followed by the group of countries that had joined the EU before 2000 (Austria, Denmark, Finland, Greece, Ireland, Spain, Sweden, and the United Kingdom) and those joining after 2000 (Czech Republic, Hungary, Poland, and Romania). The lowest sales rates were seen among the combined group of four non-EU countries (Norway, Russia, Switzerland, and Turkey). By 2005, an estimated total of 308,000 patients had received treatment with peginterferons in the 21 countries included in the study. The number of those ever treated varied widely, from a high of 16 per 100 prevalent cases in France, followed by the Czech Republic, Germany, the Netherlands, and Sweden, at between 10 and 12 per cent, to less than 1 per cent of cases in Greece, Poland, Romania, and Russia. The United Kingdom was among countries with a relatively low number of patients treated, at around 3.5 per cent, equating to the average rate in the 21 countries.

In an attempt to explain observed variations, the authors point to the potential role of financial restrictions, with sales rates found to be low in countries imposing restrictions on reimbursement of treatment costs, such as in some countries of central and eastern Europe. When considering the variation in the number of patients ever treated, Lettmeier et al. (2008) highlighted the role of under-detection of prevalent cases, citing evidence that in France, which operates an active screening policy for Hepatitis C, about 40 per cent of cases remain undetected whereas in Spain this figure is estimated at 80 per cent.[30] The authors further point to the potential impact of drug policies that might restrict access to treatment for high risk groups such as injecting drug users, although these considerations are not systematically followed up.

Table 6 Summary of studies of international variation in the use of new anti-viral drugs for the treatment of hepatitis C

Stated study objective	Study design	Year	Data source	Population/s studied	Outcome measure/s	Key findings	Notes	Source
To compare the market uptake of peginterferons across countries of the WHO European region	Pharmaco-epidemiological study of the uptake of peginterferon alpha-2a and alpha-2b	2000–2005	IMS Health database (quarterly sales data)	*EU Founding Members*: Belgium, France, Germany, Italy, and the Netherlands *EU-joiners before 2000*: Austria, Denmark, Finland, Greece, Ireland, Spain, Sweden, and the UK *EU-joiners after 2000*: Czech Republic, Hungary, Poland, and Romania *Non-EU*: Norway, Russia, Switzerland, and Turkey	Country-specific sales rates; annual number of patients treated (per population and per prevalent hepatitis C case)	Peginterferon sales varied by region, with highest sales among EU Founding Members and lowest among non-EU countries; country-specific cumulative treatment rates per 100 prevalent cases were 16 (France); 12 (Germany and Sweden); ~11.5 (Czech Rep and Netherlands); <10 (Austria); <8 (Switzerland); 6 (Norway and Spain); >2–4 (Belgium, Hungary, Ireland, Italy, and the UK); ~2 (Denmark and Finland); <2 (Greece, Poland, Romania, Russia, and Turkey)	Sales data do not necessarily reflect actual drug use; uncertainty around several assumptions underlying conversion of sales data into patient figures	[30]

CHAPTER 8 Summary and conclusions

This report reviewed the published and grey literature on international variations in the use of medicines to inform the Steering Group "Extent and Causes of International Variation in Drug Usage" to guide further analytical work on the extent and causes of international variation in drug usage.

With a focus in six (disease) areas: (1) osteoporosis, (2) atypical anti-psychotics, (3) dementia, (4) rheumatoid arthritis, (5) cardiovascular disease/lipid-regulating drugs (statins), and (6) hepatitis C; the systematic search found surprisingly few international comparative studies with a prime focus on examining the use of medicines. Studies varied widely in study design and focus, populations studied, outcomes measured, and time frames. For example, few studies examined medicines use on the basis of (prevalent) population-level data; instead they based their analysis on data from selected population sub-groups. This limits the generalisability of findings to the entire population and limits comparability to population-based analyses.

The quality of studies identified from the search varied widely, but given the scarcity of evidence available this review did not attempt to rate studies according to quality criteria. Furthermore, given the considerable variability in study design and populations studied, it was not possible to synthesise data extracted from the various studies to identify common trends or patterns within disease areas. Many studies, in particular those examining the use of atypical anti-psychotics and population-based studies of statin use, analysed data from the late 1990s and early 2000s; however, usage has changed considerably since then and it would therefore be misleading to use those early data as indicators of contemporary variation in medicines use. Instead, we will focus on common issues emerging from the evidence reviewed here in relation to the potential causes underlying observed international variation in medicines use.

At the risk of simplification, determinants of variation in medicines use may be distinguished into three broad groups: namely, macro- or system-level determinants, service organisation determinants, and clinical practice determinants. We address each of these in turn below.

8.1 Macro- or system-level determinants

These include factors acting at the level of the financing and regulation of the health system, and issues around reimbursement policies: whether a given treatment is being reimbursed under the statutory system and at what level, including patient co-payments, and national priority setting.

Differences in reimbursement policies were highlighted as a likely driving force of international variation in almost all areas of medicines use reviewed here, including dementia,[14 15] rheumatoid arthritis,[18] hepatitis C,[30] and, for some countries in central and eastern Europe, statins.[28] It was for example pointed out that the reimbursement of treatment of dementia patients in the Netherlands required a complex negation process involving clinical, biological, and radiological information for each patient,[14 15] which may explain the comparatively low use of dementia drugs in the Netherlands in the mid-2000s. Also, in 2005, of 23 European countries only half provided full reimbursement for four dementia medications (rivastigmine, galantamine, donepezil, and memantine).[15] It is worthwhile noting though that one study, when comparing statin use in Canada and Australia, did not find notable differences in use between the two regions despite differences in reimbursement systems.[25] This suggests that the role of reimbursement policies as a determinant of international variation in medicines use is likely to vary with the nature of the medicine in question and is likely to be important for high-cost medicines.

Several studies further emphasised the role of national priority setting, with for example Pariente et al. (2008) noting France's 2001 plan of action for Alzheimer's disease which is likely to have increased the number of patients receiving treatment, possibly explaining the comparatively high usage of dementia medicines in France compared with other European countries in the mid-2000s.[14] A similar reasoning has been suggested for France's comparatively high proportion of patients with hepatitis C cases receiving peginterferons compared with its European neighbours, likely to be attributable to the active screening policy for hepatitis C operated in France.[30] Jönsson et al. have highlighted the role of health technology assessments (HTAs) in the uptake of biological treatments of rheumatoid arthritis, noting that the use of health care cost approaches such as in Australia and the United Kingdom might explain the comparatively low use of biologicals in these countries compared with countries such as Norway and Sweden, which tend to combine a tradition in HTA with a societal perspective.[18]

Studies of use of biologicals for the treatment of rheumatoid arthritis further highlighted the possible role of medicines pricing to play some role in international variation in use. Thus, Kobelt and Kasteng (2009) found the higher documented sales of biologicals per patient in Germany to be a consequence of higher manufacturer prices while the proportion of patients receiving treatment was comparatively low.[16] Notably, the same study also highlighted that in the United Kingdom, sales per patient were well below average in 2008 despite the proportion of patients on treatment being similar to the European average, reflecting currency fluctuations in Pound Sterling relative to the Euro, pointing to the challenges to interpretation of national data on medicines sales in an international comparative perspective.[16]

A final point related to reimbursement policies, but rarely mentioned by studies reviewed here, is the role of patient co-payment as a potential factor explaining some of the international variation in medicines use. Duarte et al. (2007) in their analysis of women's preferences for the treatment of osteoporosis noted that the role of co-payments was generally seen as low in European countries but not so in Mexico.[6] Evidence from the United States in particular has noted the positive association between co-payments and cost-related medication underuse among patients with chronic illness,[31 32] and Cohen et al. (2007) highlighted the relatively high patient cost sharing for the large variation in the availability of medicines in the United States compared with European countries.[33] The extent to which cost-sharing policies impact on overall use of medicines in the United States in international comparison is unclear, however.[34]

8.2 Service organisation determinants

These include factors acting at the service delivery level and mainly concern issues around the availability of or access to specialists. Indeed, most studies reviewed here pointed to differences in access to specialists as a likely driver of international variation in areas such as atypical anti-psychotics,[9] dementia,[14 15] and rheumatic arthritis.[18] For example, studies highlighted that there is great variation among European countries in whether or not GPs are authorised to initiate and/or continue dementia treatment initiated by specialists.[15] Access to and availability of relevant specialists may therefore act as a crucial bottleneck for accessing treatment, and Pariente et al. (2008) argued that the "relative lack" of relevant specialists in the United Kingdom could partly explain the low levels of usage of cholinesterase inhibitor in the country.[14]

Variations in access to specialists such as rheumatologists was also put forward as an important factor determining uptake of treatment of rheumatoid arthritis; Jönsson et al. (2008) noted that the comparatively low number of rheumatologists at one rheumatologist per 150,000 population in the United Kingdom and one per 200,000 in Germany might explain the observed lower uptake of biological drugs in those countries compared with, for example, France and the United States; both these countries offer higher number of rheumatologists (1/25,000 in France and 1/ 50,000 in the United States).[18]

8.3 Clinical practice determinants

These include diagnostic patterns, prescribing behaviour, use of clinical/practice guidelines, and readiness to adopt new/innovative medicines.

Several studies reviewed here pointed to the role of variation in clinical practice as an important determinant of international variation in medicines use, noting for example differences in the use of classification systems for the diagnosis of mental disorders between the United States (Diagnostic and Statistical Manual (DSM) criteria) and European countries (International Classification of Diseases),[9] and differences in the use of clinical or practice guidelines.[12 16]

Many studies pointed to differences in prescribing patterns as an important factor, but none of those presented here provided empirical evidence to support this notion. However,

Zullino et al. (2005), in their study of psychotropic drug prescriptions in German and Swiss psychiatric hospitals, found some evidence pointing to a possible reluctance among clinicians in Germany to take up newer medicines.[11] Bhatt et al. (2005) found substantial variation in patients' medication use by physician specialty, with cardiologists prescribing statins significantly more often than other physician specialties,[27] highlighting differences in professional attitudes to treatment as a potentially important factor underlying international variation of medicines use.[28]

Clearly, these three broad categories are interrelated, with for example a readiness among clinicians to adopt innovations in routine practice determined, to some degree, by the ease by which access to innovation is provided at the system level. Likewise, use of clinical guidelines in routine practice requires the actual availability of such guidelines.

However, although each of these factors is likely to play a role in explaining international variation in medicines use, their relative importance will vary depending on the disease area in question and the system context. It is likely that any given level of use of a given medicine in one country is determined by a set of factors the combination and the relative weight of which will be different in another country.

REFERENCES

Reference List

1. Richards M. *Improving access to medicines for NHS patients: a report for the Secretary of State for Health by Professor Mike Richards.* London: Department of Health, 2008.
2. Nikolentzos A, Nolte E, Mays N. *Paying for (expensive) drugs in the statutory system: An overview of experiences in 13 countries.* [Online] Available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_089990 (accessed 17 December 2008). London: London School of Hygiene & Tropical Medicine, 2008.
3. Stargardt T. The impact of reference pricing on switching behaviour and healthcare utilisation: the case of statins in Germany. *Eur J Health Econom* in press.
4. International Osteoporosis Foundation. *Osteoporosis in the European Union in 2008: Ten years of progress and ongoing challenges*. Nyon: International Osteoporosis Foundation, 2008.
5. International Osteoporosis Foundation. *Osteoporosis in the European Union 2008. Country reports.* Nyon: International Osteoporosis Foundation, 2008.
6. Duarte J, Bolge S, Sen S. An evaluation of patients' preferences for osteoporosis medications and their attributes: the PREFER-International study. *Clin Ther* 2007;29:488-503.
7. Broekema W, de Groot I, van Harten P. Simultaneous prescribing of atypical antipsychotics, conventional antipsychotics and anticholinergics – a European study. *Pharm World Sci* 2007;29(126-130).
8. Santamaria B, Perez M, Montero D, Madurga N, de Abajo F. Use of antipsychotic agents in Spain through 1985-2000. *Eur Psychiatry* 2002;17:471-76.
9. Zito J, Safer D, de Jong-van den Berg L, Janhsen K, Fegert J, Gardnerm J, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adol Psych Ment Health* 2008;2:26-33.
10. Hübner-Liebermann B, Spiebl H, Iwai K, Cording C. Treatment of schizophrenia: implications derived from an intercultural hospital comparison between Germany and Japan. *Int J Soc Psychiatry* 2005;51:83-96.
11. Zullino D, Mayland G, Schmidt L, Fähndrich E, Greil W, Horvath A, et al. Prescribing practices in German and Swiss psychiatric university and in non-university hospitals: national differences. *Int J Clin Pharmacol Ther* 2005;43:339-49.

12. Haro J, Edgell E, Frewer P, Alonso J, Jones P, SOHO Study Group. The European Schizophrenia Outpatient Health Outcomes Study: baseline findings across country and treatment. *Acta Psychiatr Scand Suppl* 2003;416:7-15.
13. Bitter I, Chou J, Ungvari G, Tang W, Xiang Z, Iwanami A, et al. Prescribing for inpatients with schizophrenia: an international multi-center comparative study. *Pharmacopsychiatry* 2003;36:143-49.
14. Pariente A, Helmer C, Merliere Y, Moore N, Fourrier-Réglat A, Dartigues J. Prevalence of cholinesterase inhibitors in subjects with dementia in Europe. *Pharmacoepidemiol Drug Safety* 2008;17:655-60.
15. Oude Voshaar R, Burns A, Olde Rikkert M, European Dementia Consensus Network Group (EDCON). Alarming arbitrariness in EU prescription and reimbursement criteria for anti-dementia drugs. *Int J Ger Psychiatry* 2006;21:29-31.
16. Kobelt G, Kasteng F. *Access to innovative treatments in rheumatoid arthritis in Europe.* [Online] Available at: http://www.lif.se/cs/Publik%20webb/Sidinnehall/Publik_Dokument/Pressmeddelanden/Access%20to%20RA%20Treatments%20October%202009.pdf (accessed 28 December 2009).
17. Sokka T, Kautiainen H, Toloza S, Mäkinen H, Verstappen S, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007;66:1491-96.
18. Jönsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and access to treatment: uptake of new therapies. *Eur J Health Econom* 2008;8 (Suppl. 2):S61-S86.
19. Sokka T, Kautainen H, Pincus T, Toloza S, da Rocha Castelar Pinheiro G, Lazovskis J, et al. Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. *Ann Rheum Dis* 2009;68:1666-72.
20. EURO-MED STAT Group. EURO-MED-STAT: monitoring expenditure and utilization of medicinal products in the European Union countries: a public health approach. *Eur J Public Health* 2003;13 (Suppl):95-100.
21. Walley T, Folino-Gallo P, Schwabe U, van Ganse E, Group E, Stephens P. Comparison of national administrative and commercial databases to monitor expenditure and costs of statins across Europe. *Eur J Clin Pharm* 2004;60:503-11.
22. Goodman S, Huang W, Yan A, Budaj A, Kennelly B, Gore J, et al. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. *Am Heart J* 2009;158:193-201.
23. Walley T, Folino-Galllo P, Schwabe U, Van Ganse E, EuroMedStat Group. Variations and increase in the use of statins across Europe: data from administrative databases. *BMJ* 2004;328:385-86.
24. Walley T, Folino-Galllo P, Stephens P, van Ganse E, EuroMedStat Group. Trends in the prescribing and utilizaton of statins and other lipid lowering drugs across Europe 1997-2003. *Br J Clin Phamacol* 2005;60:543-51.

25. Cooke C, Nissen L, Sketris I, Tett S. Quantifying the use of the statin antilipemic drugs: comparisons and contrasts between Nova Scotia, Canada and Queensland, Australia. *Clin Ther* 2005;27:497-507.
26. Carruthers K, Dabbous O, Flather M, Starkey I, Jacob A, Macleod D, et al. Contemporary management of acute coronary syndromes: does the practice match the evidence? The global registry of acute coronary events (GRACE). *Heart* 2005;91:290-98.
27. Bhatt D, Steg P, Ohman E, Hirsch A, Ikeda Y, Mas J, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-89.
28. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovascular Prev Rehab* 2009;16:121-37.
29. Cooney M, Storey S, Taylor L, Dudina A, Hall M, Hemeryck L, et al. EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) III – A comparison of Irish and European results. *Ir Med J* 2009;102:113-16.
30. Lettmeier B, Muehlberger N, Schwarzer R, Sroczynski G, Wright D, Seuzem S, et al. Market uptake of new antiretroviral drugs for the treatment of hepatitis C. *J Hepatol* 2008;49:528-36.
31. Piette J, Heisler M, Horne R, Alexander G. A conceptually based approach to understanding chronically ill patients' responses to medication cost pressures. *Soc Sci Med* 2006;62:846-57.
32. Wagner T, Heisler M, Piette J. Prescription drug co-payments and cost-related medication underuse. *Health Econ Policy Law. 2008 Jan;3(Pt 1):51-67* 2008;3:51-67.
33. Cohen J, Faden L, Predaris S. Patient access to pharmaceuticals: an international comparison. *Eur J Health Econom* 2007;8:253-66.
34. Cohen J, Cairns C, Paquette C, Faden L. Comparing patient access to pharmaceuticals in the UK and US. *Appl Health Econ Health Policy* 2006;5:177-87.

APPENDICES

Appendix A

Extent and Causes of International Variation in Medicines Usage: Medicines considered for review

Osteoporosis	**Atypical Anti-psychotics**	**Dementia**
Alendronic Acid	Amisulpride	Donepezil
Alendronic Acid#Colecalciferol	Aripiprazole	Galantamine
Calcium#Colecalciferol#Risedronic Acid	Clozapine	Memantine
Calcium#Etidronic Acid	Olanzapine	Rivastigmine
Calcium#Risedronic Acid	Paliperidone	Combined (defined daily doses)
Etidronic Acid	Quetiapine	
Ibandronic Acid	Risperidone	
Pamidronic Acid	Sertindole	
Risedronic Acid	Ziprasidone	
Strontium Ranelate	Zotepine	
Zolendronic Acid		
Rheumatoid Arthritis	**Statins**	**Hepatitis C**
Abatacept	Atorvastatin	Peginterferon Alfa
Adalimumab	Fluvastatin	Peginterferon Alfa
Anakinra	Lovastatin	Peginterferon Alfa
Etanercept	Pravastatin	Peginterferon Alfa
Infliximab	Rosuvastatin	
	Simvastatin	
	Ezetimibe	

Appendix B

Search strategy: Osteoporosis

("2000"[Publication Date]: "3000"[Publication Date]) AND (("alendronate"[MeSH Terms] OR "alendronate"[All Fields]) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms])))

Number of records: 317

Search strategy: Atypical anti-psychotics

("2000"[PDAT]: "3000"[PDAT]) AND ((atypical[All Fields] AND ("antipsychotic agents"[MeSH Terms] OR ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic agents"[All Fields] OR "antipsychotics"[All Fields] OR "antipsychotic agents"[Pharmacological Action])) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms])) AND (international[All Fields] OR cross-national[All Fields] OR cross-country[All Fields] OR ("europe"[MeSH Terms] OR "europe"[All Fields]) OR Americ$[All Fields]))

Number of records: 205

Search strategy: Dementia

("donepezil"[Substance Name] OR "donepezil"[All Fields]) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]))

Number of records: 217

Search strategy: Rheumatoid arthritis

(("abatacept"[Substance Name] OR "abatacept"[All Fields]) OR ("adalimumab"[Substance Name] OR "adalimumab"[All Fields])) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]))

Number of records: 262

("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) AND ("biology"[MeSH Terms] OR "biology"[All Fields] OR "biological"[All Fields]) AND (("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields]) OR drug[All Fields] OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]))

Number of records: 281

(("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND international[All Fields]

Number of records: 448

Search strategy: Statins

("hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statins"[All Fields] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action]) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR usage[All Fields] OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields])) AND (international[All Fields] OR ("europe"[MeSH Terms] OR "europe"[All Fields]) OR comparison$[All Fields]) AND ("2000/02/10"[PDat]: "2010/02/06"[PDat])

Number of records: 964

Search strategy: Hepatitis C

("2000"[PDAT]: "3000"[PDAT]) AND (("hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statins"[All Fields] OR "hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action]) AND (("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]) OR ("utilization"[Subheading] OR "utilization"[All Fields]) OR ("economics"[MeSH Terms] OR "economics"[All Fields] OR "consumption"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms])) AND international[All Fields])

Number of records: 91