

Inpatient Drug Utilization in Europe: Nationwide Data Sources and a Review of Publications on a Selected Group of Medicines (PROTECT Project)

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Abstract: Drug utilization (DU) studies in inpatient settings at a national level are rarely conducted. The main objective of this study was to review the general information on hospital medicine management in Europe and to report on the availability and characteristics of nationwide administrative drug consumption databases. A secondary objective was to perform a review of published studies on hospital DU of a group of selected drugs, focusing on methodological characteristics (ATC/DDD). General information on hospital drug management was retrieved from several websites, nationwide administrative drug consumption databases and reports published by governmental organizations. A PubMed search was conducted using keywords related to the selected group of drugs AND 'hospital drug utilization'. The data sources for hospital DU information varied widely and included 14 databases from 25 reviewed countries. Bulgaria, Croatia, Denmark, Estonia, Finland, France, Hungary, Iceland, Latvia, Norway and Sweden obtain information on inpatient DU at a national level from wholesalers/manufacturers. In Belgium, Italy and Portugal, drugs dispensed to patients in hospitals are registered at a national level. Data are freely available online only for Denmark and Iceland. From the PubMed search, of a total of 868 retrieved studies, only 13 studies used the ATC/DDD methodology. Although the number of DDD/100 bed-days was used in four studies, other units of measure were also used. The type of information provided for the inpatient sector allowed primarily for conducting DU research at an aggregated data level. The existence of national administrative structures to monitor hospital DU would contribute to promoting the rational use of medicines and improving the safety and quality of prescribing.

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) is a project co-ordinated by the European Medicines Agency (EMA) that began on 1 September 2009. The overall objective was to 'strengthen the monitoring of the benefit–risk of medicines in Europe' [1]. Within the framework for pharmacoepidemiological studies, one aim is to review and compile knowledge regarding European sources of data on drug utilization (DU) in outpatient and inpatient healthcare settings.

Over the last 30 years, hospital pharmacy services have changed their role from the preparation of medicines to a more patient-centred service that covers all aspects related to the safety, effectiveness and economical use of medicines in a

hospital [2]. To achieve these goals, the monitoring of DU patterns at a hospital level is essential, and electronic medical records or claims data are required as data sources for inpatient pharmacoepidemiological research.

Very few countries have an organized system to collect inpatient DU at a national level [3,4] despite the fact that medicines prescribed in hospitals affect outpatient prescription and total pharmaceutical expenditure [5,6]. Inpatient medicine expenditure ranges from 8% of the total pharmaceutical expenditure in Germany to 35% in Denmark and Spain [7].

Information on drug use during patients' hospital stays will provide more accurate data for benefit–risk estimation [1,8]. Therefore, the PROTECT project focuses on five pairs of drug-adverse events to explore the feasibility of using different types of DU data sources to provide accurate data for a benefit–risk assessment [9].

The main objective of this study was twofold: to review the general information on hospital medicines management in Europe and to report on the availability and characteristics of

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nationwide data sources in Europe. A secondary objective was to perform a review of published studies on hospital DU of the group of selected drugs for the PROTECT project, focusing on methodological characteristics (ATC/DDD), to provide current information regarding hospital DU research for these selected drugs for future hospital DU research.

Methods

To achieve the main objective, we searched two potential sources of information on DU hospital settings: general information available on the internet through nationwide administrative drug consumption databases and nationwide institutional information; additionally, we conducted a literature review using an electronic bibliographic database (PubMed) for the second objective.

General internet information. We conducted an Internet search in a hierarchical manner, from institutional European websites to governmental websites. We also searched Google (no date limits) and free-access websites that did not require registration or passwords. There were no language restrictions. Informal contacts and interviews with European experts in the field of DU research completed this search. No attempt was made to perform a systematic review.

We extracted general information on hospital medicine management and consumption from the Pharmaceutical Health Information System (PHIS) website [10]. Through links from the PHIS website and the information contained in its report (PHIS Pharma Report) [7], three other websites were identified: the European Association of Hospital Pharmacists (EAHP) website [11], the European Hospital and Healthcare Association (HOPE) website [12] and the Organization for Economic Cooperation and Development (OECD) website [13].

Nationwide administrative drug consumption databases and nationwide institutional information. We defined nationwide administrative drug consumption databases as those population-based databases supported by governmental organizations, health insurance companies or sickness funds, all of which collect information on medicine sales at the manufacturer or wholesaler levels and/or at the pharmacy level.

As part of the inventory on nationwide administrative drug consumption databases developed by the PROTECT Working Group on DU [3,4], information on drug consumption data in the inpatient sector was previously available for 14 countries.

In addition, we developed a questionnaire with the intention of collecting information on the items considered relevant when measuring drug exposure for the inpatient sector in the nationwide administrative drug consumption databases [3,4].

We also explored whether the National Medicines Agencies' websites had published reports on inpatient DU.

Bibliographic search. The Anatomical Therapeutic Chemical (ATC) codes of the selected drugs for the PROTECT project included are as follows: C08, calcium channel blockers; N03A, anti-epileptics; N05BA, benzodiazepine derivatives (anxiolytics); N05CD, benzodiazepine derivatives (hypnotics and sedatives); N06A, antidepressants; N06CA, antidepressants in combination with psycholeptics; R03AC, selective beta-2-adrenoreceptor agonists; and R03AK, adrenergics in combination with other drugs for obstructive airway diseases. All active pharmaceutical ingredients classified at ATC level five of these groups were included. The reason for the selection of these groups of medicines has been described elsewhere [9].

Antimicrobials, which are also included in the PROTECT project, were excluded because the reasons for the study of their consumption

in hospital settings are well known [10,,14,15]. Most European countries support antibiotic resistance surveillance programmes, and antibacterial consumption has been widely studied [16,17].

A search in PubMed was conducted. Each drug in the medicine group (calcium channel blockers, anti-epileptics, beta-2-agonists, antidepressants and benzodiazepines) was combined with 'hospital drug utilization' using the Boolean logic AND. The search was conducted in March 2011 and updated in September 2014. The setting was the European geographical area.

The titles retrieved in the search were included if they had been published since 1980, were set in any European hospital (for this study, inpatient DU covered nursing homes, psychiatric clinics and any other institution categorized as a long-term care unit), provided that one of their objectives was to review the patterns of DU [18]. Any article published in a language understood by any of the group members was included: English, Spanish or any other Romanic language or Scandinavian languages. No restrictions regarding the type of study design were imposed.

Studies were excluded if the medicines were dispensed from the hospital pharmacy to outpatients. Duplicates and references for which an abstract was not available were also excluded from the review.

All units and methods of measurement were valid for the review. Those abstracts classifying medicines according to the ATC codification [18] and/or quantifying drug use in defined daily doses (DDDs) were selected and are described in table 3.

Results

We present the results in two parts referring to the two objectives of this paper.

Hospital information: general information, sources and characteristics of hospital nationwide DU data.

From the PHIS website [10], the last hospital report published in 2010 could be freely downloaded [7]. It reported on European inpatient pharmaceutical consumption, which was expressed as percentages of total pharmaceutical consumption. Inpatient drug consumption ranged from 3% of the total drug consumption in Sweden to 14% in Latvia. On average, 30–40% of hospitals had an available hospital pharmacy. The percentage of hospital pharmacies per total number of hospitals varied from 2% in Finland (the number of pharmacies in small hospitals or dispensaries was unknown) to 100% in Portugal and Romania, where all public hospitals must have a hospital pharmacy. Pharmaceutical provision in hospitals without a pharmacy was assured by other hospital pharmacies or by community pharmacies. The number of substances included in the therapeutic formularies ranged from 100 in small Finish hospitals to 1500 in Austrian hospitals [7].

There were also specific country PHIS hospital pharma reports for Austria, Belgium Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Slovakia, Sweden, the Netherlands and the United Kingdom that were published between 2009 and 2011 [19].

From the EAHP [11], we retrieved the report on a survey conducted in 2010 in 1283 hospitals from 30 European countries [20]; this survey is updated every 5 years. It provides information on the organization and activities of European

hospital pharmacies in the 27 European Member States but does not contain information on DU.

From the *OECD website* [13], a technical report on the use of hospital administrative databases in health research was downloaded. The report provides information on the types of data collected by different national hospital administrative databases in different OECD countries (including non-EU countries) [21].

From the inventory of nationwide administrative drug consumption databases included in the PROTECT project [3,4], 14 databases from 25 reviewed countries (Belgium, Bulgaria, Croatia, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Iceland, Ireland, Latvia, Lithuania, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland, the Netherlands and the United Kingdom) offered available information of inpatient drug consumption.

Among the 14 European countries with information on hospital DU (Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Hungary, Italy, Iceland, Latvia, Norway, Portugal and Sweden), only Denmark had the volume of medicines sold and distributed by hospital ward freely available on the Danish Registry of Medicinal Products Statistics website [22]. From national reports on DU published by national organizations, France, Norway, Bulgaria, Croatia, Estonia, Latvia and Finland provided data on the volume of medicines sold by wholesalers to hospitals. Belgium has a national inpatient drug dispensation database. In Italy, the information on medicines dispensed to patients while in the hospital is registered in regional databases, and that information is sent to the Italian Medicines Agency. Portugal collects information on medicines dispensed to patients while in the hospital, and this information includes the inpatient drug consumption definition and the medicines prescribed and supplied by the hospital to the outpatient [3,4]. Additionally, information on wholesalers' sales was available. In Sweden, hospital drug consumption up to 2013 was collected by the Apotekens Service, and this information is currently collected by the government agency eHälsomyndigheten, in which non-prescription sales are considered for those used in hospitals and other health institutions. Those data are available upon request. In Iceland, the wholesaler consumption data do not distinguish between outpatient and in hospital; these data are freely available (for a display of information on the hospital databases, see table 1).

All databases except those in Sweden and Belgium had nearly 100% population coverage and used the ATC/DDD methodology (table 1). In Sweden, because of changes in the distribution channel of medicines, the current database population coverage is unknown. Since 2013, hospitals have been free to organize their own drug supply without using a licensed pharmacy, and it is not compulsory for the county authorities to report the sales to the government agency.

Bibliographic search.

All available abstracts retrieved by the search in PubMed were reviewed to see whether they fulfilled the inclusion criteria.

Because the search strategy did not take into account the indication for the use of the medicines, several articles were found to qualify under the antidepressant, anti-epileptic or benzodiazepine categories. A flow chart has been prepared for each group of medicines (see table 2 and supplementary material).

The articles excluded on the grounds of lacking DU research studies were either studying the metabolism of the active pharmaceutical ingredient in animals or the guidelines of the use of the drugs in clinical practice.

Of the 82 included studies, 13 used the ATC/DDD methodology (table 2 and table 3). The characteristics of the 13 studies are described in table 3. It is important to stress that only five of the 13 articles monitored DU in more than one hospital, and three of the studies included nursing homes. Only one article compared hospital medicine consumption in one hospital between two countries.

The sources of the DU information varied widely among the 13 articles. Clinical records or pharmacy drug records were the most commonly used sources, but nursing files, hospital pharmacy sales, patient interviews and request forms for drug monitoring were also used.

Although the number of DDD/100 bed-days was used as a unit of measurement in four studies, other studies used the percentage of users, the prescribed daily dose (PDD), DDD, DDD/1000 inhab/day, the number of patients receiving an active ingredient or the percentages of active ingredients out of the total consumption of the main anatomical group and the number of users or prescriptions (table 3).

Discussion

A review of information on hospital DU at a national level in Europe including the availability of nationwide administrative drug consumption databases and a review of published inpatient DU studies of a group of selected drugs was presented in this study. There has not yet been any such review on these subjects.

The information retrieved from general information websites reflected the heterogeneity in the management of medicines at a hospital level and provided technical information on hospital administrative organization in Europe.

From the review of nationwide administrative drug consumption databases, it can be observed that most of the countries provide data on the volume of medicines sold by wholesalers to hospitals, whereas Portugal, Italy and Belgium collect information on medicines dispensed to patients during their hospital stay [3,4]. Regarding data accessibility, only Denmark and Iceland have hospital DU data freely available.

Figures reflecting DU research and patterns of drug use in inpatient settings at a national level in Europe are sparse, which was reflected in the scope of the articles retrieved from the PubMed search. Most of the reviewed articles focused on patterns of DU within one hospital or several hospitals within a single country.

The PubMed search also showed that there was variety in units of measurement used. Although WHO recommends

Table 1.

National public databases providing information on hospital drug consumption in Europe.

Countries	Belgium	Bulgaria	Croatia	Denmark	Estonia	Finland
Database name	Minimum basic dataset (MBDS)	Not provided	Not provided	Register of medicinal products statistics	SAM Database	Drug sales register
Data provider	Federal Public Service (FPS) Health, Food Chain Safety and Environment	Bulgarian Medicines Agency	Croatian Drug Agency	Danish Health and Medicines Authority	State Agency of Medicines	Finnish Medicines Agency
Website	http://www.health.belgium.be/eportal/Healthcare/Healthcarefacilities/Registrationsystems/index.htm	http://en.bda.bg/	www.almp.hr	http://sundhedsstyrelsen.dk/	www.sam.ee	www.fimea.fi
Accessibility	adhoc_admDM@sante.belgique.be	Application Medicines use control department maria.popova@bda.bg	Application viola.malocic@halmed.hr	Free online www.medstat.dk Further data upon request	Application ott.laius@ravimiamet.ee	Applications communications@fimea.fi
Data source	Prescribed and dispensed	Sales	Sales	Sales	Sales	Sales
Population coverage	21.5% of hospitals	100%	100%	100%	100%	100%
Data by age/gender	Yes	No	No	Yes	No	No
Record linkage	Yes	No	No	Yes	No	No

¹Includes medicines prescribed and supplied by the hospital to outpatient.

defined daily doses [23] adjusted by the hospital clinical activity (bed-days) [24], we noted that a high variability in the quantification of medicines was used, and the most commonly used measurement was the percentage of users or the percentage of the active ingredient. This could be because the information on the number of beds or hospital occupancy rates may not be available at the national or local level. In our bibliographic search, most of the studies mentioned the drugs included in the study without mentioning a specific classification system, and those studies using the ATC system were limited.

Commercial companies such as IMS Health, Inc. (originally known as Intercontinental Marketing Services) have established a hospital database (Hospital Prescribing Audit Index) that reflects the consumption of medicines sold into and distributed by hospital pharmacies [3,25]; however, this type of database is beyond the scope of this MiniReview.

Several factors may explain the scarcity of DU data in the inpatient healthcare sector for the studied drugs: the high heterogeneity in the management and financing of medicines at the hospital level, the availability of a hospital drug formulary, the distribution chain of the medicines and whether a hospital

pharmacy is present or the number of pharmacy technicians per inhabitant [7].

This scarcity in inpatient DU research, particularly when comparing patterns of medicine use across several countries, is opposed to the outpatient sector, in which most European countries keep an updated nationwide administrative drug consumption database of prescribed and/or reimbursed medicines. Many hospitals have monitoring systems because they have computer registration systems; however, because these computer systems are not compatible between hospitals, it is not possible to integrate this information at a national level [7].

In some countries, such as Spain, it has been established in the laws that health authorities must centralize DU information from the hospitals throughout the country [26]; however, this information is not collected. In other countries, such as the UK, an initiative is ongoing for the development of a new software system to pull data from different hospital pharmacy computer systems to a central server to create a national database [27]. At the subnational level, there is a hospital utilization database (HUDB) in Scotland with the overall objective of providing access to staff in NHS Boards and

France	Hungary	Italy	Iceland	Latvia	Norway	Portugal	Sweden
ANSM database	Not provided	OsMED database	Not provided	Not provided	Wholesalers drug statistics	Infarmed database	Under restructuration since January 2014 Apoteket AB database up to 2013
The French National Agency for Medicines and Health Products Safety (ANSM)	Directorate General of National Institute of Pharmacy	Italian Medicines Agency	Icelandic Medicine Agency	State Medicines Agency of Latvia	Norwegian Institute of Public Health	National Medicines Agency	Ehalsomyndigheten since January 2014. National Corporation of Swedish Pharmacies up to 2013
www.ansm.sante.fr	www.ogyi.hu	http://www.agenziafarmaco.gov.it/en	www.imca.is	http://www.zva.gov.lv/	www.fhi.no	www.infarmed.pt	http://www.ehalsomyndigheten.se/
Application communication@ameli.fr	Application ogyi@ogyi.hu	Application farmaci line@aifa.gov.it	Free online http://www.imca.is/imca/statistics/nr/235	Application info@zva.gov.lv	Application lmfin@fhi.no	Application dempsamps@infarmed.pt	Application: registrator@ehalsomynidigheten.se
Sales	Sales	Dispensed	Sales	Sales	Sales	Prescribed Dispense ¹	Sales
100%	100%	100%	100%	100%	100%	100%	100% up to 2013.
No	Yes	Yes	Yes	No	Yes	No	Yes
No	No	Yes at regional level	No	No	No	No	No

other interested parties to deliver high-level information to support the assessment and monitoring of costs and clinical effectiveness of medicines used in hospitals. The data contained in the HMUD can be integrated to provide reports at the hospital level and can be aggregated up to the NHS Board and/or Cancer Network [28].

Certain elements within the included studies make it difficult to compare hospital DU across countries. The distinction between what is considered outpatient and inpatient consumption varies: some countries may include medicines prescribed to outpatients by specialists and medicines prescribed in nursing homes, psychiatric clinics or other institutions with long-term inpatient care as inpatient consumption [7,29].

Cross-national differences in hospital definitions can lead to differences in drug consumption; this is known as the ambulatory care/hospital care bias.

For the future, the challenge will be to contribute more clinical content to hospital national drug consumption data collection and to provide compatible computer systems. This would provide the opportunity for a combined analysis at the country level and the European level and would allow for intra- and intercountry comparisons. Improvement is required to build national administrative structures to monitor hospital DU, which will contribute to promoting the rational use of medicines and improving the safety and quality of prescribing medicines [29].

Table 2.

Studies reviewed and included.

	Calcium channel blockers	Anti-epileptics	Antidepressants	Benzodiazepines	Beta2-adrenergics	Total
Citations	155	243	312	292	44	996
Abstracts reviewed	134	194	295	253	42	868
Included	6	14	26	36	0	82
ATC/DDD	1	3	5	4	0	13

Table 3.

Information from the included studies using ATC/DDD methodology.

Reference	Number and			Source of information	Units of measurement	Drugs	ATC Coding system	Population source
	Countries	type of hospitals	Period					
Calcium channel blockers								
Lucena <i>et al.</i> J ClinPharmacol 2003 [31]	Spain	25 hospitals	Feb–June 1999	Patient and family interview, Written medication plan	% PDD/DDD Number of prescriptions Number of patients	Insulins, oral blood glucose-lowering drugs, antithrombotic agents, cardiac glycosides, antihypertensives (Calcium channel blockers, ACE and angiotensin II inhibitors, beta-blockers, others), corticosteroids for systemic use, systemic hormonal preparations, antibacterials, musculoskeletal system, analgesics, anti-epileptics, psycholeptics, psychoanaleptics, anti-asthmatics	Yes	Patients admitted to gastrointestinal and liver departments with a diagnosis of liver cirrhosis
Antidepressants								
Rapp MA <i>et al.</i> PsychiatrPrax 2010 [32] (abstract)	Germany (Berlin)	18 nursing homes	Not reported	Not reported	Number of DDDs	Psychotropics	No	Residents with dementia in nursing homes Entire country
Divac N <i>et al.</i> Pharmacoepidemiol Drug Saf 2006 [33]	Serbia and Montenegro	Hospital (1) and ambulatory	2000–2004	Wholesale data, Institute of Mental Health	DDD per 1000 inhabitants per day, number of DDDs per 100 bed-days	Antidepressants, antipsychotics and anxiolytics/hypnotics	Yes	
Barbui C <i>et al.</i> Eur Arch Psychiatry Clin Neurosci 2005 [34]	Italy (South-Verona)	Inpatient unit located in the general hospital	1981/1982, 1991/1992, 2001/2002	Clinical records	Sum PDD/DDD ratio, Number of patients receiving psychotropic drugs	Antidepressants, antipsychotics and benzodiazepines	No	All patients consecutively admitted to the inpatient unit
Rytter E, Tidsskr Nor Laegeforen 2003 [35] (abstract)	Norway	20 psychiatric hospitals or psychiatric units and general hospitals	1991–2000	Hospital pharmacy sales	Number of DDDs per 100 patient days	Antidepressants, antipsychotics and benzodiazepines	Yes	Inpatient

Table 3. (continued)

Reference	Countries	Number and type of hospitals	Period	Number of patients included	Source of information	Units of measurement	Drugs	ATC Coding system	Population source
Sorensen L <i>et al.</i> Int J Geriatr Psychiatry 2001 [36]	Denmark (Northern Jutland)	12 randomly selected nursing homes	1 February-1 July 1995	288	Nurses files	Median and mean DDDs, % of users, median duration of intake	Antidepressants, neuroleptics and benzodiazepines	Yes	Danish-speaking permanent residents aged 65 years and older
Benzodiazepines Azermat M <i>et al.</i> Hum Psychopharmacol Clin Exp 2011 [37]	Belgium	76 randomly selected nursing homes	2005	1730	Medical charts	Per cent use of all residents	Antipsychotics, benzodiazepine hypnotics, sedatives and anxiolytics, benzodiazepine related Z-drugs, antidepressants and antimentia drugs	Yes	Nursing home residents for whom clinical information was available and who were not in palliative or terminal care
Stolker JJ <i>et al.</i> Gen Hosp Psychiatry 1998 [38]	The Netherlands	1 (2 Intensive Care Units, ICUs)	1 st January-31 st March 1995	137	Medical records	Number and % of users, Average daily dose (DDDs/day)	Benzodiazepines, antipsychotics, antidepressants	Yes	Patients ≥18 years admitted to two general ICUs
Petit N <i>et al.</i> Pharm World Sci, 1994 [39] (<i>abstract and methods section</i>)	Belgium (Liège)	1 (635-bed teaching hospital)	1991 (February, May, August and November)	4307 patient drug records	Drug records, pharmacy department	DDD per 100 bed-days, number of prescriptions, compared with calculated mean prescribed daily doses (PDD)	Benzodiazepine hypnotics and anxiolytics	Yes	All admitted patients during the defined period

Table 3. (continued)

Reference	Countries	Number and type of hospitals	Period	Number of patients included	Source of information	Units of measurement	Drugs	ATC Coding system	Population source
Bergman U <i>et al.</i> Eur J Clin Pharmacol 1980 [40] (abstract)	Sweden	1 university hospital	1975–1977	Not reported	Drug delivery and prescription data	DDD/bed-day	Hypnotics, sedatives and minor tranquilizers	No	All admitted patients to the departments of Paediatrics, Medicine, Pneumology, Allergy, Neurology, General surgery, Transplant surgery, Urology, Orthopaedics, Gynaecology and Obstetrics, Ophthalmology, Oto-rhino-laryngology, Psychiatry
Anti-epileptics Korísková B <i>et al.</i> Ther Drug Monit, 2006 [41] (abstract)	Czech Republic Sweden	1 (Ostrava University Hospital) 1 (Huddinge)	1993–2004 (Ostrava), 1995–1999 (Huddinge)	2824 1268	Not reported	PDD	Anti-epileptic (N03A)	Yes	Adult outpatients in Ostrava, adult out- and inpatients in Huddinge
Korísková B <i>et al.</i> Int J Pharmacol Ther, 2006 [42] (abstract)	Czech Republic	1 (Ostrava University Hospital)	1993–2004	1144	Request and replay forms for therapeutic drug monitoring	PDDs (plasma levels)	Anti-epileptic (N03A)	Yes	Adult inpatients
Prpic I <i>et al.</i> Eur J Neurol, 2005 [43]	Croatia	1 (Hospital Centre Rijeka)	2001–2002	Not reported	Hospital pharmacy record	Number of DDDs per 100 bed-days	Anti-epileptic (N03A)	Yes	Patients admitted to Departments of Neurology, Paediatrics, Psychiatry and Neurosurgery

PDD/DDD, prescribed daily dose/Defined Daily Dose, DDD, defined daily dose, ICU, intensive care unit.

A review of the use of hospital databases in observational studies has been recently published [8]. The authors selected the published studies using hospital databases and focused on DU and prescribing practices. They found two European databases containing information on hospital drug use for a sample of hospitals: GIFA from Italy (which includes eight adhered hospitals) and PHARMO (a multiple linked database covering three million inhabitants in the Netherlands). Our PubMed search did not include any observational studies conducted with those databases because they did not focus on the drugs of interest for the PROTECT project.

Strengths: We offer an overview of the existing websites of general information regarding medicine hospital management. These data have been retrieved from three reports [7,20,21] that were published relatively recently; therefore, the information provided is current.

This MiniReview provides a brief summary of the availability of hospital DU data sources at a national level in Europe and contains information retrieved from websites, published reports and nationwide administrative drug consumption databases. In addition, information on DU studies of a selected group of drugs for the PROTECT project was provided from the PubMed search. A systematic search for in-hospital sources of DU and a review for a selected group of drugs assist in understanding the situation of in-hospital medicine use throughout Europe.

In addition, the PubMed search revealed the scarcity of studies on inpatient patterns of DU for selected compounds at a national level in Europe and demonstrated the practical non-existence of studies comparing the consumption of the selected group of drugs across countries and over time. The detailed information included in studies that use the ATC/DDD methodology would allow the possibility of conducting Cross-National comparisons and highlights some of the gaps in DU research in hospital settings.

There are several limitations to this review.

Regarding the general internet information, there was no attempt to perform a complete and systematic review. The extracted information represents the authors' opinions.

With respect to the search on nationwide administrative drug consumption databases, several issues should be noted. The search was based on information available on the inventory in a national drug consumption database that was first published in 2011 and has been updated annually since then with the inclusion of information from new European countries.

There are also some limitations in the literature review: firstly, only one bibliographic database, PubMed, was used. This may have introduced a bias towards studies published in English [30]. Secondly, the search strategy did not include synonyms, MeSH terms or truncations; therefore, there is the possibility that articles not indexed according to the terms specified in the search may have been excluded. However, the use of such broad terms should allow for retrieving a high number of studies. Thirdly, because the search focused on selected drugs analysed in the PROTECT project, which are mainly used in the outpatient setting, other groups of drugs were not included. Therefore, studies focusing on those drugs

may have been missed. Finally, the articles were included on the basis of what was stated in the abstract. The study design, the drugs under study and the methodology included are clearly stated in an abstract; thus, we do not believe we have missed any articles, and those using the ATC/DDD methodology were fully reviewed when possible.

In conclusion, our MiniReview adds information on hospital DU data in Europe. In contrast to the outpatient healthcare sector, in which nationwide administrative drug consumption databases are widely available, the inpatient healthcare sector does not utilize such a national administrative structure to monitor DU, which makes research in this area difficult. In addition, several other factors make it difficult to monitor inpatient DU and conduct Cross-National comparison studies: the classification of drugs, the definition of inpatient healthcare, the units of measurement, the hospital medicine management and the availability of a hospital pharmacy. Some of these factors reflect the healthcare system and policies of the countries. This MiniReview provides insight into the gaps that must be addressed to advance DU research in hospital settings.

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References

- PROTECT. PROTECT Project. <http://www.imi-protect.eu/July2014>.
- Mossialos E, Mrazek M, Walley TE. Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. First. Open University Press, England, 2004;213–26.
- Ferrer P, Sabaté M, Petri H, Goh KL, Yeboa S, Solari P, Ibáñez L; on behalf of the PROTECT project BE. Drug Consumption Databases in Europe. http://www.imi-protect.eu/documents/DUinventory_2013_year4_Dec2013.pdf. December 2014.
- Ferrer P, Ballarín E, Sabaté M, Laporte J-R, Schoonen M, Rottenkolber M *et al.* Sources of European drug consumption data at a country level. *Int J Public Health* 2014;**59**:877–87.
- MacFarlane J, Holmes WF, MacFarlane R. Do hospital physicians have a role in reducing antibiotic prescribing in the community? *Thorax* 2000;**55**:153–8.
- Bradley CP. Factors which influence the decision whether or not to prescribe: the dilemma facing general practitioners. *Br J Gen Pract.* 1992;**42**:454–8.
- Vogler S, Habl C, Leopold C, Mazag J, Morak SZN. PHIS Hospital Pharma Report. 2010.
- Larsen MD, Cars T, Hallas J. A MiniReview of the Use of Hospital-based Databases in Observational Inpatient Studies of Drugs. *Basic Clin Pharmacol Toxicol.* Research Unit of Clinical Pharmacology, University of Southern Denmark. Nordic Pharmacological Society, Odense, Denmark, 2012.
- Abbing-Karahagopian V, Kurz X, de Vries F, Reynolds R, Klungel O. Bridging differences in findings from observational pharmacoepidemiological studies: the design and rationale of Working Package 2 of the PROTECT project. *Pharmacoepidemiol Drug Saf.* 2011;**20**:S34.
- PHIS - Pharmaceutical Health Information System. <http://whocc.goeg.at/> December 2014.
- Home | European Association of Hospital Pharmacists. <http://www.eahp.eu/July2014>.
- HOPE European Hospital and Healthcare Federation. <http://www.hope.be/July2014>.
- Organisation for Economic Co-operation and Development. <http://www.oecd.org/July2014>.
- Filius PM, Liem TB, van der Linden PD, Janknegt R, Natsch S, Vulto AG *et al.* An additional measure for quantifying antibiotic use in hospitals. *J Antimicrob Chemother.* Department of Medical Microbiology and Infectious Diseases, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. p.filius@erasmusmc.nl; 2005 May;**55**: 805–8.
- Davey P, Brown E, Fenelon L, Finch R, Gould I, Holmes A *et al.* Systematic review of antimicrobial drug prescribing in hospitals. *Emerg Infect Dis.* 2006;**12**:211–6.
- Aldeyab MA, Kearney MP, McElnay JC, Magee FA, Conlon G, Gill D *et al.* A point prevalence survey of antibiotic prescriptions: benchmarking and patterns of use. *Br J Clin Pharmacol.* Clinical and Practice Research Group, School of Pharmacy, Queen's University Belfast, Belfast, BT9 7BL, UK. maldeyab02@qub.ac.uk; The British Pharmacological Society; 2011 Feb;**71**:293–6.
- Elseviers MM, Ferech M, Vander SR, Goossens H; group E project. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. *Pharmacoepidemiol Drug Saf.* Faculty of Medicine, Division of Nursing and Midwifery, University of Antwerp, Antwerp, Belgium.: John Wiley & Sons, Ltd; 2007;**16**:115–23.
- WHO, editor. Introduction to Drug Utilization Research. World Health Organization, Oslo, Norway, 2003. <http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf>/July 2014.
- WHOC Publications Country reports. <http://whocc.goeg.at/Publications/CountryReports/July2014>.
- Frontini R, Miharija-Gala T, Sykora J. EAH Survey 2010 on hospital pharmacy in Europe: Part 1. General frame and staffing. *Eur J Hosp Pharm Sci Pract* 2012;**19**:385–7.
- P M. Using hospital administrative databases for a disease-based approach to studying health care systems. 2001. <http://www.oecd.org/sweden/1889879.pdf>/July 2014.
- Statistics TDR of MP. MEDSTAT.DK Statens Serum Institut - Statistikker. <http://medstat.dk/en/July2014/July2014>.
- WHO Collaborating Centre for Drug Statistics and Methodology. <http://www.whocc.no/July2014>.
- Dukes MNG ed. Drug Utilization Studies. Methods and Uses. Dukes MNG, editor. WHO Regional Publications, Finland, European Series, No45; 1993.
- IMS Health <http://www.imshealth.com/portal/site/ims/July2014>.
- <http://www.boe.es/boe/dias/2014/03/25/pdfs/BOE-A-2014-3189.pdf> (Sec. I. P'g. 26396)/October 2014.
- Anonymous. Changes in medication management are key, hospital pharmacists hear at Dublin conference. *HPN Hospital Pharmacy News.* Dublin; Issue 7, 22. http://issuu.com/pharmacynewsireland/docs/hpn_7_lores/24/October2014.
- ISD Scotland. Hospital Medicines Utilization. <http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Hospital-Medicines-Utilisation/October2014>.
- Vander Stichele RH, Elseviers MM, Ferech M, Blet S, Goossens H, Group EP. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. *Br J Clin Pharmacol* 2004;**58**:419–28.
- Wong SS-L, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment

- studies and systematic reviews in MEDLINE and EMBASE. *J Med Libr Assoc.* 2006 ;**94**:451–5.
- 31 Lucena MI, Andrade RJ, Tognoni G, Hidalgo R, de Sanchez ICF; Diseases SCSG on TM of L. Drug use for non-hepatic associated conditions in patients with liver cirrhosis. *Eur J Clin Pharmacol.* 2003;**59**:71–6.
- 32 Rapp MA, Majic T, Pluta J-P, Mell T, Kalbitzer J, Treusch Y *et al.* [Pharmacotherapy of neuropsychiatric symptoms in dementia in nursing homes: a comparison of service provision by psychiatric outpatient clinics and primary care psychiatrists]. *Psychiatr Prax [Internet].* 2010;**37**:196–8.
- 33 Divac N, Tosevski DL, Babic D, Djuric D, Prostran M, Samardzic R. Trends in consumption of psychiatric drugs in Serbia and Montenegro 2000–2004. *Pharmacoepidemiol Drug Saf.* 2006;**15**:835–8.
- 34 Barbui C, Ciuna A, Nose M, Levi D, Andretta M, Patten SB *et al.* Drug treatment modalities in psychiatric inpatient practice: a 20-year comparison. *Eur Arch Psychiatry Clin Neurosci.* 2005;**255**:136–42.
- 35 Rytter E, Häberg M. [Utilization of psychopharmaceuticals in Norwegian psychiatric hospitals 1991–2000]. *Tidsskr Nor Lægeforen.* 2003;**123**:768–71.
- 36 Sorensen L, Foldspang A, Gulmann NC, Munk-Jorgensen P. Determinants for the use of psychotropics among nursing home residents. *Int J Geriatr Psychiatry.* 2001 Feb;**16**:147–54.
- 37 Azermai M, Elseviers M, Petrovic M, Van Bortel L, Vander Stichele R. Geriatric drug utilisation of psychotropics in Belgian nursing homes. *Hum Psychopharmacol.* 2011;**26**:12–20.
- 38 Stolker JJ, Heerdink ER, Pullen SE, Santman FW, Hekster YA, Leufkens HG *et al.* Determinants of psychotropic drug usage in a general intensive care unit. *Gen Hosp Psychiatry.* 1998 Nov;**20**:371–6.
- 39 Petit N, Delporte JP, Anseau M, Albert A, Jeusette F. Drug utilization review of oral forms of benzodiazepines in a Belgian 635-bed teaching hospital. *Pharm World Sci.* 1994;**16**:181–6.
- 40 Bergman U, Christenson I, Jansson B, Wiholm BE. Auditing hospital drug utilisation by means of defined daily doses per bed-day. A methodological study. *Eur J Clin Pharmacol.* 1980;**17**:183–7.
- 41 Koristkova B, Sjöqvist F, Grundmann M, Bergman U. The use of TDM data to assess the validity of defined daily doses of antiepileptics: a comparison between a Czech and Swedish University Hospital. *Ther Drug Monit.* 2006;**28**:589–93.
- 42 Koristkova B, Grundmann M, Brozmanova H. Differences between prescribed daily doses and defined daily doses of antiepileptics—therapeutic drug monitoring as a marker of the quality of the treatment. *Int J Clin Pharmacol Ther.* 2006;**44**:438–42.
- 43 Prpic I, Vlahovic-Palcevski V, Skarpa-Prpic I, Palcevski G, Boban M. Analysis of antiepileptic drugs use at a university hospital in Croatia. *Eur J Neurol.* 2005 Jun;**12**:483–5.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Flow chart calcium channel blockers and hospital drug utilization.

Fig. S2. Flow chart hospital drug utilization and antiepileptics.

Fig. S3. Flow chart hospital drug utilization and antidepressants.

Fig. S4. Flow chart hospital drug utilization and benzodiazepines.

Fig. S5. Flow chart hospital drug utilization and beta-2-agonists.