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SPECIAL ARTICLE

The intriguing future of pharmacoepidemiology

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Abstract Over the years more and more data have become available in the constantly growing databases on prescription drugs. This has facilitated the development of pharmacoepidemiology, a dynamic research field that has undergone a more rapid development than many other research areas. There are several reasons why pharmacoepidemiology will remain recognized as one of the most dynamic and challenging research areas of clinical pharmacology. The data explosion in modern society will continue, and observational studies aimed at assessing the value of medicines will be increasingly requested by payers, professionals and patients. Future studies in pharmacoepidemiology must include specialist drugs used in the hospital setting and also be designed to address obstacles hindering the delivery of effective medicines to the patient. Pharmacoepidemiological methods may also be valuable tools to address new challenges, such as the environmental impact of medicines. A potential threat is that the increasing amounts of data available in registries may add fuel to the debate on confidentiality. The too strict application of privacy rules might hinder the further development of pharmacoepidemiology.

Keywords Pharmacoepidemiology · Drug utilization · Databases · Observational studies · Future

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Introduction

In the beginning, there was nothing. No data were available to study the prescribing and use of drugs. Over the years more and more data have become available in the constantly growing databases on prescription drugs. This has facilitated the development of pharmacoepidemiology. During the last 50 years this research area has developed from descriptive studies counting tablets to advanced analytical models to assess the effectiveness and safety of drug therapy in clinical practice. Clinical pharmacologists have played an important role in this development and their engagement will be important for future development of the field.

Pharmacoepidemiology—the bridge between clinical pharmacology and epidemiology

Pharmacoepidemiology can be defined as the study of the use and the effects of drugs in large numbers of people [1]. The research area can be seen as the bridge between clinical pharmacology and epidemiology (Fig. 1). Clinical pharmacology, with its pharmacokinetic and pharmacodynamic principles, contributes towards an understanding of the relationship between drug exposure and response in humans. Epidemiology, on the other hand, contributes with various descriptive and analytical methods. Clinical pharmacologists have also brought the concepts of critical drug evaluation and rational use of drugs into the research field. This dual background, with pharmacoepidemiology acquiring its focus of inquiry from clinical pharmacology and its methods of inquiry from epidemiology, has created a dynamic research field undergoing a more rapid development than many other research areas.

The birth of pharmacoepidemiology may be dated to the early 1960s [1, 2]. Growing concerns about adverse drug

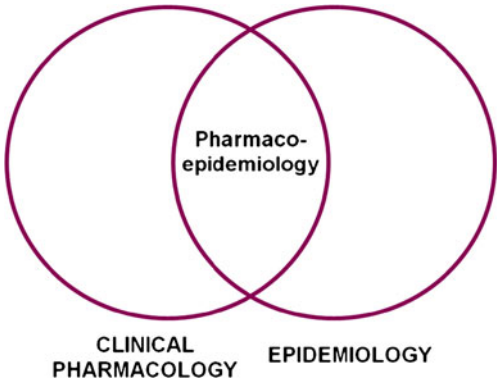

Fig. 1 Pharmacoepidemiology—the bridge between clinical pharmacology and epidemiology

reactions (ADRs) emphasized the need to develop methods to study the safety of drug therapy. The thalidomide disaster in the late 1950s and early 1960s strengthened the requirements for the pharmaceutical industry to provide proof of the safety of their drugs before approval [1]. In 1960, the Federal Drug Administration (FDA) started collecting ADR reports, leading to the establishment of hospital-based drug monitoring programs. These systems were further developed, and the term pharmacoepidemiology was proposed for the new discipline [2].

At the same time in Europe, clinical pharmacologists were conducting pioneering drug utilization studies. Many of these studies focused on differences in the utilization of drugs between countries or regions and were based on existing data sources [3–11]. Other pioneering studies focused on factors influencing the prescribing patterns of physicians [12]. Originally, drug utilization research was defined as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences" [13]. The main difference between drug utilization and pharmacoepidemiology was that the latter focused to a greater extent on the quantitative benefits and risks of drug treatment in cohorts of patients, while drug utilization focused more on drug exposure and differences in the quality and quantity of drug use [14, 15]. During the last decades of the 20th century, pharmacoepidemiology shifted from being focused entirely on ADRs and risk association studies to also include other clinical outcomes and health economic aspects of drug use, thereby lessening the distinction between pharmacoepidemiology and drug utilization research.

Clinical pharmacologists discovered very early the potential of drug utilization research in promoting rational prescribing. In their contribution to "Avery's drug treatment", Folke Sjöqvist et al. suggested that rational drug prescribing involves: a decision on whether to use a drug, and if so, the selection of a suitable drug and regimen; consideration of compatibility between the drug and patient and any other drugs being given; a legibly written prescription; and appropriate instruction(s) to the patient about the use of the drug and the expectations of treatment and follow-up [16]. Drug utilization studies were designed to assess these aspects of rational prescribing, and the research area has provided important tools to identify areas of irrational prescribing, forming the basis for guideline development and policy decisions [17–21].

Most prophecies have been fulfilled

People have always been intrigued of what the future will look like. Pharmacoepidemiologists share these interests, and there have been many predictions about the future over the years since the discipline was formed. In 1990, Strom and Tugwell summarized the achievements during the first decades and made a number of predictions for the future [22]. At that time, the quite young discipline had already shown its ability to contribute to the rational use of drugs, and a number of possible approaches to detecting and evaluating adverse drug reactions had been developed. The first databases of medical claims information had been developed, and the first universities had started pharmacoepidemiology training programs. Strom and Tugwell predicted a rapidly increasing interest in pharmacoepidemiology and that it would have an increasing impact on clinical medicine [22].

In 1995, Alvarez and Porta reviewed the opinions of leading pharmacoepidemiologists on the prospects of pharmacoepidemiology and summarized the most important challenges the discipline would face on its way towards the next century [23]. The future was expected to bring many opportunities, including the growth of databases, the development of methods and an increased international collaboration. The introduction of computer-assisted decision algorithms to reduce the level of uncertainty in decision-making was suggested. Certain challenges were also noted, including the limited number of qualified professionals, the difficulties in using administrative databases for research purposes (including restrictions due to confidentiality) and the lack of appropriate measures to assess the benefits of drug therapy in observational studies. Still, the expectation was that pharmacoepidemiology would meet the requirements of modern society to improve medication safety. Academic researchers, regulators and the pharmaceutical industry were pointed out as the key stakeholders in this process, but the need to establish a link between pharmacoepidemiology and economics was also emphasized [23, 24].

Most of the prophecies above have been fulfilled. In less than 50 years, pharmacoepidemiology has undergone a rapid development, similar to development of epidemiology (Table 1) [25].

Table 1 Threads in the fabric of the development of pharmacoepidemiology

- Quantitative reasoning
- Comparative studies of drug utilization in different settings
- Development of classification systems and measurement units [e.g. the Anatomical, Therapeutic and Chemical (ATC) classification system and the Defined Daily Dose (DDD)]
- Claims databases and registries
- Biostatistics methods
- (Personal) computers
- User-friendly statistical software
- Biotechnology revolution
- Information technology
- Genomics

The predicted data explosion has become a reality. Progress in computer technology has allowed rapid access to descriptive data that in the early days were time consuming to collect and compile. Databases based on administrative claims data or medical records were established in North America and Europe [26–32]. The first Nordic population-based pharmacoepidemiological databases were established in Sweden in the 1970s [15]. Today, all Nordic countries have established population-based registries covering all dispensed drugs to their entire respective population [33]. An increasing number of healthcare organizations in North America, Europe and Asia have established large datasets on prescribed or dispensed drugs—in many cases with the possibility of linkage to clinical data in other registries [34–37].

In many countries, disease-based registers have been established for the specific reporting of clinical information and management of certain diseases and procedures [38]. The potential for analyzing the effects and safety of drugs has further developed with the introduction of electronic health records containing not only prescription drug data but also other clinical parameters, such as diagnosis, vital signs, laboratory data and more or less structured clinical notes [39]. In some countries, biobanks have also been established enabling linking drug utilization to genetic data [33, 40].

Bias and confounding are still great challenges

The increasing amount of data does not imply that studies have become easier to conduct. In many databases, registration is incomplete and, therefore, there is the potential for bias [41–43]. Furthermore, healthcare data are difficult to analyze due to the large number of variables and the interrelated nature of these variables. These challenges have been addressed in some reviews on how to use administrative data for pharmacoepidemiological research [41–43].

Pharmacoepidemiological studies are generally subject to three sources of bias; information bias, selection bias and confounding (Table 2) [44, 45].

A particular problem with pharmacoepidemiological studies is the potential for confounding by indication, due to the fact that the drug may have been prescribed to patients having, a priori, a higher or lower risk of presenting the event studied [46]. Potential factors influencing the decision to prescribe—thus potentially leading to confounding-by-indication—may vary by physician and over time and involve a mix of clinical, functional and behavioral patient characteristics [39]. The Channeling of drug prescribing to certain patients may also occur as a result of guidelines or reimbursement restrictions favoring certain drugs.

While randomization balances the groups with respect to both known and unknown covariates, observational studies are limited with respect to the latter, making confounding an important issue. The development of new techniques, such as propensity scores and other matching algorithms, has enabled studies handling large numbers of potential confounders [39, 47, 48]. In theory, many confounding factors unknown today could—with the discovery of the human genome—be identified, taken into account and adjusted for [47, 49]. This was suggested by Concato and Horwitz who set up the ambitious goal "to conquer confounding by 2015" and noted that it might be within our reach, since "the number of pertinent factors is likely to be smaller than the 3 billion base-pairs in the human genome" [49]. However, this goal was suggested 9 years ago, and 2015 is now rapidly approaching, with confounding still far from being conquered. Most stakeholders still consider observational studies to be less reliable than clinical trials, and a recent review found no evidence of any shift in recognition of observational studies by the Cochrane Collaboration [50].

Drug utilization research has developed beyond descriptive studies

The area of drug utilization research has also developed beyond the descriptive studies that dominated the field during the first years. Folke Sjöqvist and Donald Birkett suggested that drug utilization research could be divided into descriptive and analytical studies [21]. The emphasis of the former would be to describe patterns of drug utilization and to identify problems deserving more detailed studies. Analytical studies, on the other hand, would link drug utilization data to figures on morbidity, outcome of treatment and quality of care, with the ultimate goal being to assess whether drug therapy is rational or not. Analytical drug utilization studies could also be designed to assess potential explanatory factors behind the observed utilization patterns [20]. An increasing number of drug utilization studies published today are just such analytical

Table 2 Bias and confounding in pharmacoepidemiological studies[a]

Source of bias	Description of bias source
Information bias (misclassification)	Distortion of the estimate of the association between a risk factor (e.g. use of a drug) and the occurrence of an event, due to a systematic difference in the way information concerning the measured parameter is collected for the groups being compared.
	Information bias may be either non-differential or differential. Non-differential misclassification may occur if there is the same probability of being misclassified for all study subjects and may lead to an underestimation of the hypothesized relationship between exposure and outcome. Differential misclassification may occur when the error rate or probability of being misclassified differs across groups of study subjects and may lead to wrong conclusions.
Selection bias	Distortion of the estimate of the association between a risk factor (e.g. use of a drug) and the occurrence of an event, resulting from the measurements made in a sample which is not representative of the population to which the results are to be extrapolated. Some examples include admission bias, diagnostic bias and survival bias.
Confounding	Systematic error resulting from the fact that a secondary variable is linked both to the exposure and the event of interest, which can wholly or partially explain their association found in an epidemiological study.

[a] For a more detailed description, the reader is referred to references [44] and 45]

studies, and many of these apply record-linkage with other data. Another positive development is the increased number of studies focusing on the patient's perspective, taking advantage of existing databases to follow dispensing histories in patients over time [51].

Today, drug utilization data are routinely used to promote rational prescribing in many hospitals and to assess the clinical appropriateness, cost effectiveness and, in some cases, outcome of therapy. Drug utilization data are also increasingly used in ambulatory care as a benchmarking tool and in educational interventions to prescribing physicians [52]. In recent years, regulations have been strengthened in many countries linking data to financial incentives and paying physicians for reaching identified targets [52]. The wider role of drug utilization research in health policy corresponds well to the more recent proposed definition of the research area: "Drug Utilization Research is an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes". [20].

Finally, it is important to emphasize that drug utilization research also includes qualitative studies to provide a deeper understanding of the subjective aspects of prescribing, dispensing and utilization of drugs and the interaction between healthcare providers and patients [20]. Such studies are also extremely important for the deeper understanding of medication use in the society, but these will not be covered in this paper.

The intriguing future

Pharmacoepidemiology has undergone a rapid development that will continue during the 21th century. About 2500 years ago the Chinese philosopher Confucius stated that "If a man take no thought about what is distant, he will find sorrow near at hand." Consequently, it may be wise to make some predictions about the future and the important challenges that will have to be met.

In the future—all drugs will be monitored post-launch

The availability of electronic healthcare databases will enable researchers to identify a growing number of cases in which effectiveness does not match efficacy [53]. This will challenge the actions of all concerned—industry, regulators, payers and healthcare providers. Risk management plans (RMPs) or risk evaluation and mitigation strategies are already required by European Medicines Agency and FDA as part of the medicine approval process to help ensure that the benefits of a particular medicine outweigh its risks [54, 55]. Observational studies will also be increasingly requested by reimbursement agencies and other payers to assess the value of medicines. It is also likely that patients will demand better systems to monitor effectiveness and safety. In the future, it is therefore likely that all new drugs will be monitored post-launch. This monitoring may range from descriptive drug statistics to sophisticated comparative effectiveness studies, depending on the budget impact and level of uncertainty about the benefit–risk of the medicine (Fig. 2). The difficulties conducting studies also indicate that the nature of the monitoring activities will be limited by the availability of data and competent pharmacoepidemiologists.

Descriptive statistics are already being used in most countries to monitor the introduction of new medicines. Diffusion patterns of new drugs may be compared with existing alternatives, often stratified by age, gender and geography. Without patient identity data, the number of defined daily doses (DDD)/1000 inhabitants/day or

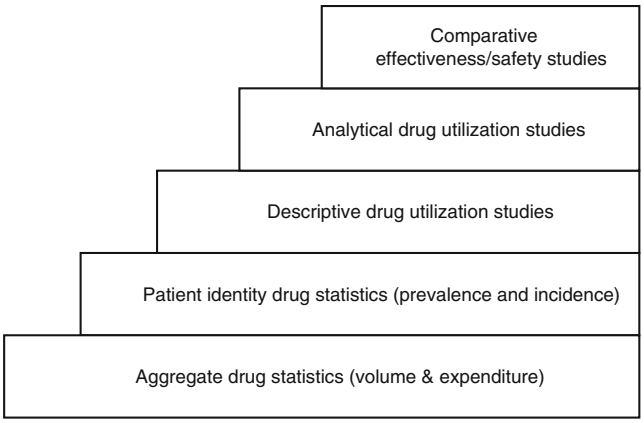

Fig. 2 Different types of monitoring of new medicines with increasing levels of complexity

DDD/100 bed-days can be used as rough estimate of the proportion of the population exposed [14]. The opportunities increase dramatically with the availability of encrypted patient identifiers, facilitating studies of the prevalence and incidence of drug use [33, 56]. Patient identity drug data, with or without record-linkage, may also be used to identify if the utilization is appropriate, i.e., to what extent patients prescribed the drug correspond to the labeled indication, the reimbursed indication or the patient groups for which there are evidence of efficacy in clinical trials. In these studies, relevant patient characteristics (e.g. age, gender, co-morbidity, disease status and concomitant drug therapy) may be analyzed for those initiated on the drug and potentially compared with those initiated on other drugs. Although crude, such analyses may be a valuable tool to estimate the likely risk–benefit of the drug when used in clinical practice.

Payers will also increasingly require health economic studies to assess the cost-effectiveness of the new premium priced therapies compared to the existing standards. Increasing difficulties for national health services financing new expensive therapies will lead to the development of various risk-sharing models. This has been defined as 'agreements concluded by payers and pharmaceutical companies to diminish the impact on payers' budgets for new and existing schemes brought about by uncertainty and/ or the need to work within finite budgets' [57]. Such agreements can include financially based schemes, such as price–volume agreements or performance-based/ outcomes-based schemes. The latter includes schemes whereby pharmaceutical companies refund monies where the new drug does not achieve the desired outcomes [57].

It is essential that the increasing amounts of data collected to monitor the utilization, effectiveness and safety of new medicines will be used to improve clinical decision-making. Avorn and Fisher reviewed current barriers to the dissemination of recommendations and proposed a number of solutions, including more effective educational outreach programs, requirements for practitioners to master important findings and alignment of incentives to encourage evidence-based practice [58].

New therapeutic areas needs to be addressed

The majority of pharmacoepidemiological studies performed today are based on data generated in ambulatory care [59]. This is also the case for drug utilization studies. A recent literature study found that one-third of all European cross-national comparative studies of drug utilization conducted between 2001 and 2011 examined antibiotic use [60]. Other common areas were cardiovascular drugs and those drugs acting on the nervous system. A similar pattern was observed in a review of pharmacoepidemiological studies conducted in the Nordic countries between 2005 and 2010, with the most commonly studied drugs being those acting on the nervous system, including psychotropic drugs, analgesics, antiepileptics and drugs for dementia and Parkinson's disease (Wettermark et al, The Nordic Prescription Databases as a resource 690 for pharmacoepidemiological research—a literature review, Under Review). Many studies were also conducted on cardiovascular drugs, such as antihypertensives and lipid-lowering agents, as well as on drugs acting on the alimentary tract, including antidiabetic agents and proton pump inhibitors (Wettermark et al, The Nordic Prescription Databases as a resource 690 for pharmacoepidemiological research—a literature review, Under Review). This dominance may partly be attributable to data availability, with most databases being restricted to prescription drugs dispensed and/or reimbursed to outpatients [59]. However, the drug market is rapidly changing, with more and more new drugs being introduced onto the market for the treatment of cancer and autoimmune diseases [61, 62]. Consequently, the future of pharmacoepidemiology must include more studies conducted in the hospital setting.

It may also be wise to look at the World Health Organization's report entitled "Priority Medicines for Europe and the World," which identifies a number of gaps for diseases for which treatments do not exist, are inadequate or are not reaching patients [63] (Table 3). The authors recommend that pharmaceutical innovation be encouraged by a shorter medicine development process, a reviewed reimbursement procedure and a more attractive research environment [63]. Pharmacoepidemiology could contribute to better treatment in these areas, particularly in addressing obstacles where effective medicines could be better delivered to the patient. The report also highlights the special needs of three population groups (elderly, women and children) which should be addressed. Pharmacoepidemiology will be an important tool here, and efforts are now underway to use data from automated databases to conduct observational studies on drug use in children [64]. Similar strategies are urgently needed for the elderly, especially in light of demographic trends in Europe [65].

Table 3 Priority disease areas for which treatments do not exist, are inadequate or are not reaching patients[a]

- Future public health threats: infections due to antibacterial resistance, pandemic influenza
- Diseases for which better formulations are required: cardiovascular disease (secondary prevention); diabetes; postpartum hemorrhage, pediatric HIV/AIDS, depression in the elderly and adolescents
- Diseases for which biomarkers are absent: Alzheimer disease; osteoarthritis
- Diseases for which basic and applied research is required: cancer; acute stroke
- Neglected diseases or areas: tuberculosis; malaria and other tropical infectious diseases such as trypanosomiasis, leishmaniasis and Buruli ulcer, HIV vaccine
- Diseases for which prevention is particularly effective: chronic obstructive pulmonary disease including smoking cessation; alcohol use disorders: alcoholic liver diseases and alcohol dependency

HIV/AIDS, Human immunodeficency virus/acquired immune deficiency syndrome

[a] Data in table are extracted from the World Health Organization's report "Priority Medicines for Europe and the World" [63]

The future will also bring an increased focus on the impact of drugs on our environment. Since the 1990s water contamination by pharmaceuticals has been an issue of concern [66]. Most pharmaceuticals are deposited in the environment through human consumption and excretion. The term "pharmacoenvironmentology" has been proposed for the science dealing with the environmental impact of drugs given to humans and animals at therapeutic doses, and "ecopharmacovigilance" as the science and activities associated with the detection, evaluation, understanding and prevention of the adverse effects of pharmaceuticals in the environment [67]. Pharmacoepidemiology could help these young disciplines by contributing important methods and concepts.

Further battles on confidentiality may arise

We have been fortunate to live in an era where large amounts of data have become available for research. It is important to recognize, however, that the increasing amounts of sensitive data available in registries may add fuel to the debate on confidentiality. Based on the Declarations of Helsinki from the World Medical Association, it is a basic right of the patient to be assured that all of his/her medical and personal data are confidential [68]. Researchers active in the field have recognized these ethical issues and adopted methods to ensure that the confidentiality of individually identifiable data is maintained [69]. However, the way forward has not always been easy, with years of discussions on the usefulness and integrity of collecting and storing personal data in some countries. The European Commission has recently proposed a stronger and more coherent data protection framework for the European Union [70]. Hopefully, this will not prevent/hinder the opportunities for conducting research. A too strict application of privacy rules might hinder the further development of pharmacoepidemiology.

The golden days are here to stay

There are several reasons why pharmacoepidemiology will remain to be recognized as one of the most dynamic and challenging research areas of clinical pharmacology. The data explosion in modern society will continue. By the end of 2010, one-half a zettabyte (unit of information equal to 10^{21} bytes) of data traveled across the Internet, which is equivalent to the information contained on a bookshelf 36 billion miles long (10-fold the distance from Earth to Pluto) [71]. And every 5 min, digital data are created equivalent to all of the information stored in the U.S. Library of Congress [72]. Considerable amounts of healthcare data will also be generated, including data used in various electronic decision-support systems [73]. Some data will be unstructured and tricky to analyze, but new techniques and methods will be developed to confront those challenges. The advanced biostatistics methods have no doubt been important for the scientific rigor in the field, but it is also important to acknowledge that they have added to the complexity, sometimes making it difficult for clinicians to understand and critically evaluate the methods applied.

Pharmacoepidemiology is also likely to continue to be an arena for collaboration between different stakeholders, including physicians, regulators, payers, manufacturers and the general public. Clinical pharmacologists played an important role in the birth and development of pharmacoepidemiology, and clinical pharmacologists have all the prerequisites to be the most important player in the future as well. It is important to recognize the multidisciplinary and multiprofessional nature of the research area, and it is likely that the future success will require alliances to other professions, including specialists within specific clinical areas but also those involved in health economy and health policy. Twenty years ago, Brian Strom stated that pharmacoepidemiology needed better science, better scientists, more science and more scientists [74]. This statement is still very relevant, although it is important to acknowledge the progress that has been made during the first 50 years of pharmacoepidemiology.

A final wish for the future is that pharmacoepidemiology and drug utilization will take further steps beyond the description and identification of problems to providing tools for improvement in drug utilization. No one knows what the future will bring, but it is obvious that those of us active in the field may look forward to interesting times. It is strange to imagine that one day we will call this period for "the good old days."

Acknowledgments I met Folke Sjöqvist, for the first time in 1991 when he was professor of clinical pharmacology and chair

of the Drug and Therapeutics Committee at Huddinge University hospital. I had just graduated from the school of Pharmacy and started to work as a hospital pharmacist with one of my main tasks to produce drug utilization reports to the hospital clinics and the Drug and Therapeutics Committee. It aroused my interest in pharmacoepidemiology, and I became affiliated to clinical pharmacology as a doctoral student subsequently defending a PhD. I wish to thank Folke, but also my former supervisor professor Ulf Bergman and the head of the hospital pharmacy Dr Anita Berlin for bringing me in to the intriguing research field of pharmacoepidemiology.

Conflict of interest None.

References

1. Strom BL, Kimmell SE, Hennessy S (eds) (2012) Pharmacoepidemiology, 5th edn. Wiley, Malden
2. Lawson DH (1984) Pharmacoepidemiology: a new discipline. Br Med J 289:940
3. Engel A, Siderius P (1968) The consumption of drugs. Report on a study, 1966-1967 (EURO 3101). WHO Regional Office for Europe, Copenhagen
4. Bergman U, Elmes P, Halse M, Halvorsen T, Hood M, Lunde PKM, Sjöqvist F, Wade OL, Westerholm B (1975) The measurement of drug consumption. Drugs for diabetes in Northern Ireland, Norway and Sweden. Eur J Clin Pharmacol 8:83–89
5. Sjöqvist F (1975) Drug utilization. In: Mattils MJ (ed) Proc 6th Int Congress of Pharmacology, vol 5 (clinical pharmacology). Finnish Pharmacological Society, Helsinki, pp 39–50
6. Grimsson A, Idänpään Heikkilä J, Lunde PKM, Olafsson O, Westerholm B (1979) The utilization of psychotopic drugs in Finland, Iceland, Norway and Sweden. Studies in drug utilization. WHO Regional Publications. European Series No 8. World Health Organization. Regional Office for Europe. Copenhagen
7. Stika L (1983) Patterns in drug utilization—national and international aspects: antidiabetic drugs. Acta Med Scand 105[Suppl 683]:53–57
8. WHO Drug Utilization Research Group (DURG), Griffiths K, McDevitt DG, Andrew M, Baksaas I, Lunde PK, Bergman U, Wessling A, Sjoqvist F (1985) Validation of observed differences in the utilization of antihypertensive and antidiabetic drugs in Northern Ireland, Norway and Sweden. Eur J Clin Pharmacol 29:1–8
9. WHO Drug Utilization Research Group (DURG), Griffiths K, McDevitt DG, Andrew M, Baksaas I, Helgeland A, Jervell J, Lunde PK, Oydvin K, Agenas I, Bergman U et al (1986) Therapeutic traditions in Northern Ireland, Norway and Sweden: I. Diabetes. Eur J Clin Pharmacol 30:513–519
10. WHO Drug Utilization Research Group (DURG), Griffiths K, McDevitt DG, Andrew M, Baksaas I, Helgeland A, Jervell J, Lunde PK, Oydvin K, Agenas I, Bergman U et al (1986) Therapeutic traditions in Northern Ireland, Norway and Sweden: II. Hypertension. Eur J Clin Pharmacol 30:521–525
11. Westerholm B (1986) Therapeutic auditing at the national and international level. Br J Clin Pharmacol 22:55S–59S
12. Stolley PD, Lasagna L (1969) Prescribing patterns of physicians. J Chron Dis 22:395–405
13. World Health Organization (WHO) (1977) The selection of essential drugs. Technical Report Series No. 615. World Health Organization, Geneva
14. World Health Organization (WHO) (2003) Introduction to drug utilisation research, NLM classification WB 330. World Health Organization, Oslo
15. Bergman U (2001) Pharmacoepidemiology—from description to quality assessment. A Swedish perspective. Norwegian J Epidemiol (Norsk Epidemiologi) 11:31–36
16. Sjöqvist F, Borgå O, Dahl M-L, Orme MLE (1997) Fundamentals of clinical pharmacology. In: Speight TM (ed) Avery's drug treatment, 4th edn. Adis Press, Auckland, pp 1–73
17. Laporte JR, Porta M, Capella D (1983) Drug utilization studies; a tool for determining the effectiveness of drug use. Br J Clin Pharmacol 16:301–304
18. Sjöqvist F, Agenäs I (eds) (1983) Drug utilization studies: implications for medical care. Proceedings from ANIS symposium, Sånga-Säby, Sweden. Acta Med Scand 105 [Suppl 683]
19. Lee D, Bergman U (2000) Studies of drug utilization. In: Strom BL (ed) Pharmacoepidemiology, 3rd edn. John Wiley, Chichester, pp 463–481
20. Wettermark B, Vlahovic-Palcevski V, Salvesen Blix H, Rønning M, Vander Stichele RH (2008) Drug utilization research. In: Hartzema AG, Tilson HH, Chan KA (eds) Pharmacoepidemiology and therapeutic risk assessment. Harwey Whitney Books, Cincinatti, pp 159–195
21. Sjöqvist F, Birkett D (2003) Drug utilization. In: Du Souich, Orme M, Erill S (eds) The IUPHAR compendium of basic principles for pharmacological research in humans. IUPHAR Pubications, Irvine, pp 76–84
22. Strom BL, Tugwell P (1990) Pharmacoepidemiology: current status, prospects, and problems. Ann Intern Med 113:179–181
23. Alvarez-Requejo A, Porta M (1995) Pharmacoepidemiology in practice. Current status and future trends. Drug Safety 13:1–7
24. Spitzer WO (1991) Drugs as determinants of health and disease in the population. An orientation to the bridge science of pharmacoepidemiology. J Clin Epidemiol 44:823–830
25. Schoenbach VJ (2003) Understanding the fundamentals of epidemiology: an evolving text. Learning material from the Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill. Available from: http://www.epidemiolog.net/. Accessed 20 Feb 2013
26. Malcolm E, Downey W, Strand LM, McNutt M, West R (1993) Saskatchewan Health's linkable data bases and pharmacoepidemiology. Post Market Surveill 6:175–264
27. Saunders KW, Stergachis A, Von Korff M (1994) Group health cooperative of Puget sound. In: Strom BL (ed) Pharmacoepidemiology, 2nd edn. John Wiley & Sons, West Sussex, pp 171–185
28. Friedman GD (1994) Kaiser Permanente medical care program: Northern California and other regions. In: Strom BL (ed) Pharmacoepidemiology, 2nd edn. John Wiley & Sons, West Sussex, pp 187–197
29. Carson JL, Strom BL (1994) Medicaid databases. In: Strom BL (ed) Pharmacoepidemiology, 2nd edn. John Wiley & Sons, West Sussex, pp 199–216
30. Leufkens HG, Urquhart J (1994) Automated record linkage and other approaches to pharmacoepidemiology in the Netherlands. In: Strom BL (ed) Pharmacoepidemiology, 2nd edn. John Wiley & Sons, West Sussex, pp 231–244
31. García Rodríguez LA, Pérez Gutthann S (1998) Use of the UK general practice research database for pharmacoepidemiology. Br J Clin Pharmacol 45:419–425
32. Evans JM, MacDonald TM (1999) Record-linkage for pharmacovigilance in Scotland. Br J Clin Pharmacol 47:105–110
33. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT (2010) The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 106:86–94
34. Takahashi Y, Nishida Y, Asai S (2012) Utilization of health care databases for pharmacoepidemiology. Eur J Clin Pharmacol 68:123–129

35. European Drug Utilization Research Group (2011). European Cross-National Comparison of Drug Utilisation activities. Publication from the European scientific meeting of Drug Utilization "Better public health through pharmacoepidemiology and quality use of medicine", Antwerp, Belgium 2011. Available from: http://www.pharmacoepi.org/eurodurg/workgr/Eurodurg_meeting_CNC_2011.pdf. Accessed 20 Feb 2013
36. PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (2012). Drug consumption databases in Europe. Master document, updated October 2012. Available from: http://www.imi-protect.eu/frameworkRep.shtml. Accessed 20 Feb 2013
37. Kimura T, Matsushita Y, Yang YH, Choi NK, Park BJ (2011) Pharmacovigilance systems and databases in Korea, Japan, and Taiwan. Pharmacoepidemiol Drug Saf 20:1237–1245
38. Larsson S, Lawyer P, Garellick G, Lindahl B, Lundstrom M (2012) Use of 13 disease registries in 5 countries demonstrates the potential to use outcome data to improve health care's value. Health Aff (Millwood) 31:220–227
39. Schneeweiss S (2007) Developments in post-marketing comparative effectiveness research. Clin Pharmacol Ther 82:143–156
40. Allen N, Sudlow C, Downey P, Peakman T, Danesh J, Elliott P, Gallacher J, Green J, Matthews P, Pell J, Sprosen T, Collins R, on behalf of UK Biobank (2012) UK biobank: current status and what it means for epidemiology. Health Policy Technol 1:123–126
41. Sorensen HT, Sabroe S, Olsen J (1996) A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol 25:435–442
42. Schneeweiss S, Avorn J (2005) A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 58:323–337
43. Harpe SE (2009) Using secondary data sources for pharmacoepidemiology and outcomes research. Pharmacotherapy 29:138–153
44. Begaud B (2000) Dictionnary of pharmacoepidemiology. John Wiley, Chichester
45. Porta M (ed) (2008) A dictionary of epidemiology, 5th edn. Oxford, Oxford University Press
46. Walker AM (1996) Confounding by indication. Epidemiology 7:335–336
47. Suissa S (2009) Statistical methods in pharmacoepidemiology: advances and challenges. Stat Methods Med Res 18:3–6
48. Seeger JD, Williams PL, Walker AM (2005) An application of propensity score matching using claims data. Pharmacoepidemiol Drug Saf 14:465–476
49. Concato J, Horwitz RI (2004) Beyond randomised versus observational studies. Lancet 363:1660–1661
50. Kongsted HC, Konnerup M (2012) Are more observational studies being included in Cochrane reviews? BMC Res Notes 5:570
51. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM (2008) The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract 62:76–87
52. Wettermark B, Jacobsson B, Godman B, Haaijer-Ruskamp F (2009) Soft regulations in pharmaceutical policymaking—an overview of current approaches and their consequences. Appl Health Econ Health Policy 7:1–11
53. Eichler HG, Abadie E, Breckenridge A, Flamion B, Gustafsson LL, Leufkens H et al (2011) Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. Nat Rev Drug Discov 10:495–506
54. European Medicines Agency (2005) The European Medicines Agency's (EMA) guideline on risk management systems for medicinal products for human use. European Medicines Agency, London
55. The U.S. Food and Drug Administration Amendments Act of 2007. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. Accessed 20 March 2013
56. Hallas J, Støvring H (2006) Templates for analysis of individual-level prescription data. Basic Clin Pharmacol Toxicol 98:260–265
57. Adamski J, Godman B, Ofierska-Sujkowska G, Osinska O, Herholz H, Wendykowska K, Laius O, Jan S, Sermet C, Zara C, Kalaba M, , Gustafsson R, Haycox A, Garattini S, Gustafsson LL (2010) Risk sharing arrangements for pharmaceuticals: potential and recommendations for European payers. BMC Health Serv Res 10:153
58. Avorn J, Fischer M (2010) 'Bench to behavior': translating comparative effectiveness research into improved clinical practice. Health Aff (Millwood) 29:1891–1900
59. Larsen MD, Cars T, Hallas J (2013) A minireview of the use of hospital-based databases in observational inpatient studies of drugs. Basic Clin Pharmacol Toxicol 112:13–18
60. Gillström A, Wettermark B for the Scientific Committee of the ISPE/EuroDurg meeting in Antwerp (2011). Literature review. Cross-national comparison of DU activities. Publication from the European scientific meeting of Drug Utilization "Better public health through pharmacoepidemiology and quality use of medicine", Antwerp, Belgium 2011. Available from: http://www.pharmacoepi.org/eurodurg/workgr/Report_CNC_Literature_review.pdf. Accessed 20 Feb 2013
61. Wettermark B, Persson ME, Wilking N, Kalin M, Korkmaz S, Hjemdahl P, Godman B, Petzold M, Gustafsson LL, for the Regional Drug Expert Consortium (2010) Forecasting drug use and expenditures in a metropolitan health region. BMC Health Serv Res 10:128. doi:10.1186/1472-6963-10-128
62. Truffer CJ, Keehan S, Smith S, Cylus J, Sisko A, Poisal JA, Lizonitz J, Clemens MK (2010) Health spending projections through 2019: the recession's impact continues. Health Aff (Millwood) 29:522–529
63. Kaplan W, Laing R (2004) Priority medicines for Europe and the world project. "A public health approach to innovation". World Health Organization, Geneva
64. Verhamme K, Sturkenboom M (2011) Study designs in paediatric pharmacoepidemiology. Eur J Clin Pharmacol 67[Suppl 1[:67–74
65. European Commission (2010). Directorate General for Employment, Social Affairs and Inclusion and Eurostat. Demography report 2010—older, more numerous and diverse Europeans (20/05/2011) Available from: http://ec.europa.eu/social/main.jsp?catId=738&langId=en&pubId=5936&furtherPubs=yes. Accessed 27 Jan 2013
66. Doerr-MacEwen NA, Haight ME (2006) Expert stakeholders' views on the management of human pharmaceuticals in the environment. Environ Manag 38:853–866
67. Rahman SZ, Khan RA, Gupta V, Uddin M (2007) Pharmacoenvironmentology—a component of pharmacovigilance. Environ Health 6:20
68. Beauchamp TL, Childres JF (1989) Principles of biomedical ethics, 3rd edn. Oxford University Press, New York
69. Merz JF (ed) (2001) A survey of international ethics practices in pharmacoepidemiology and drug safety. Pharmacoepidemiol Drug Saf 10:577–708
70. European Commission (2012). Proposal for a regulation of the European parliament and of the council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)

Available from: http://ec.europa.eu/justice/data-protection/document/review2012/com_2012_11_en.pdf. Accessed 10 Feb 2013
71. Wray R (2009) Internet data heads for 500 billion gigabytes. The Guardian, May 18, 2009
72. Discovery Institute (2008) Discovery Institute's Technology and Democracy Project (January 29, 2008). Discovery Institute, Seattle
73. Eiermann B,Bastholm-Rahmner P, Korkmaz S, Lilja B, Veg A, Wettermark B, Gustafsson LL (2009) Knowledge databases for clinical decision support in drug prescribing—development, quality assurance, management, integration, implementation and evaluation of clinical value. In: Chiang S. Jao (ed) Clinical decision support. InTech, Vienna
74. Strom BS (1995) Pharmacoepidemiology: response to the challenge. Pharmacoepidemiol Drug Saf 4:11–14