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Use of the UK General Practice Research Database for pharmacoepidemiology

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The last decade has seen a surge in the use of computerized health care data for pharmacoepidemiology. Of all European databases, the General Practice Research Database (GPRD) in the UK, has been the most widely used for pharmacoepidemiological research. Since 1994, this database has belonged to the UK Department of Health, and is maintained by the Office of National Statistics (ONS). Currently, around 1500 general practitioners with a population coverage in excess of 3 million, systematically provide their computerized medical data anonymously to ONS. Validation studies of the GPRD have documented the recording of medical data into general practitioners' computers to be near to complete. The GPRD collects truly population-based data, has a size that makes it possible to follow-up large cohorts of users of specific drugs, and includes both outpatient and inpatient clinical information. The access to original medical records is excellent. Desirable improvements to the GPRD would be additional computerized information on certain variables and linkage to other health care databases. Most published studies to date have been in the area of drug safety. The General Practice Research Database has proved that valuable data can be collected in a general practice setting. The full potential of this rich computerized database has yet to come. This experience should serve to encourage others to develop similar population-based data in other countries.

Keywords: computerized healthcare databases, pharmacoepidemiology, research, pharmacovigilance

Introduction

The last decades have seen a surge in the use of computerized health care data in observational drug epidemiology [1, 2]. A number of databases have been used extensively, primarily in North American countries. Pioneers have been the databases of Group Health Cooperative of Puget Sound, a Health Maintenance Organization in Washington State [3], and Saskatchewan Health of the government of the province of Saskatchewan in Canada [4]. Both databases have been used for multiple pharmacoepidemiological studies since the late seventies. Other databases used in pharmacoepidemiology are Medicaid [5, 6], and Kaiser Permanente [7] in the US.

In Europe, most countries have their populations covered through universal health care systems, an ideal situation to generate complete health care databases of all individuals included in these systems. Studies routinely based on European health computerized databases have become available only in the last decade, with resources in the UK, Netherlands and Italy [8–10]. Health care data have also been accumulated in files for a number of years in the Nordic countries [11]. However, their use by external investigators has been limited for administrative and political reasons. Of all European databases, the General Practice Research Database in the UK, has been the most widely used for pharmacoepidemiological research (see Appendix).

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History and description of the General Practice Research Database

In the UK, all health care delivery is centred around the general practitioner (GP), with referrals for specialists and for routine admission to hospital organized at the GP level. As a result of Britain's National Health Service structure, GPs maintain in their offices a complete medical history of their patients. In the late 1980s VAMP Health, a commercial company, started to install computer systems and practice management software in GPs' offices throughout the UK. From the beginning, it was foreseen that collected data could be used both for administrative and research purposes. Since 1994, the database has been known as the General Practice Research Database (GPRD), has belonged to the UK Department of Health, and is maintained by the Office of National Statistics (ONS) [12]. The costs involved in the collection of the data and the present scheme of funding of the GPRD have been reviewed elsewhere [13].

The Boston Collaborative Drug Surveillance Program (BCDSP), one of the pioneering groups in the use of automated data for pharmacoepidemiological research [14, 15] has been involved from the start in the evaluation and quality control of the GPRD, and has published a large number of papers, mainly in the area of drug safety, such as

evaluation of the risk of gastrointestinal bleeding associated with nonsteroidal anti-inflammatory drugs, acute liver injury with antibiotics, and the risk of venous thromboembolism with oral contraceptives [16].

The GPRD contains computerized information entered by GPs after a trial period of data entry and quality training. Prospective data collection is available from as early as 1987 for a limited number of practices. Starting in 1991, most practices participating in the GPRD have been providing data with the quality and completeness required for drug research projects. Currently, around 1,500 general practitioners with a population coverage in excess of 3 million, systematically provide their computerized medical data anonymously to the ONS. Upon receiving data from the GPs, ONS organizes this information and performs a series of quality checks. Data for research projects can be obtained from the ONS after review of research protocols by the Scientific and Ethical Advisory Board (SEAG). The main task of SEAG is to ensure that scientific and ethical standards are maintained, including anonymity. All information remains strictly anonymized, as no patient, general practitioner or practice identifiers are present in the data sent to investigators. The computerized information includes demographics, details of every general practitioner's consultation, a summary of specialists' clinical notes and hospital letters, results of laboratory tests and a free text section. A modification of the OXMIS classification system is used to code specific diagnoses [17], and a drug dictionary based on data from the Prescription Pricing Authority is used to code drugs. Prescriptions issued by the general practitioner are directly generated from the computer, thus ensuring a complete recording of prescriptions written by the GP, with dosage instructions included. Also, the indication for treatment is available for new courses of therapy by cross-referencing prescriptions against medical events on the same date. Recorded information can be validated and completed through review of paper-based medical records (hospital discharge letters, consultant letters, laboratory reports, etc.).

Validation studies of the GPRD have documented the recording of medical data in the general practitioners' computers to be near to complete [18, 19]. Numerous studies requiring validation of coded diagnostic outcomes have shown good agreement between the recorded diagnosis and the diagnosis on the written clinical records.

Methodological aspects: strengths and areas of improvement

Strengths

Population-based data In some of the best known automated databases, only special subsets of the general population are covered (elderly, persons with low socioeconomic status, members of private insurance plans). As the UK National Health System provides universal coverage, no segment of the population is excluded from the GPRD. In addition, all health related information from an individual is maintained by the GP, minimizing gaps in the collection of medical information. The nature of the data makes it possible to link mother and offspring information to study human reproductive epidemiology, and in particular the teratogenicity of drugs used during pregnancy [20]. The geographical distribution of the practices participating in the GPRD is representative of the UK population, apart from small variations between regions. Recent comparisons of age and sex distributions with the National Population Census have shown these to be closely similar [21].

Population large enough to study rare diseases Over 3 million persons are included in the GPRD at any one time. For most practices, data have been entered prospectively on computer for a period exceeding 5 years. In addition, many GPs have entered at their discretion historical medical data preceding prospective data recording. Data collected to date represent some 25 million person-years of information. This has allowed researchers to efficiently study rare outcomes, with an incidence rate of less than one per 10 000 persons per year, as well as chronic disorders, and conditions with short- or medium-term incubation periods.

Presence of outpatient information Most of the existing automated medical data resources include only inpatient information, or at most listings of ambulatory diagnoses recorded for reimbursement purposes. In contrast to these claims databases, one of the primary purposes of GPs' data recording is the daily clinical management of their patients. Also, one of the requirements to become a participant in the GPRD is to record all referrals to specialists as well as the information resulting from these visits. Two validation studies have documented the completeness of this information [18, 19]. In these studies, researchers reviewed information from photocopied consultant referral letters present in the offices of GPs and compared them with the diagnoses recorded in the computer files. The concordance for clinically relevant outcomes was between 90–95%. Regarding outpatient drug information, the indication for new courses of therapy is available in most instances, as well as the dosage instruction written by GPs.

Access to original medical records One of the *sine qua non* conditions to carry out valid research using automated databases is the possibility of obtaining copies of original medical records, and death certificates. Access to original records is needed in order to confirm the diagnosis initially identified through a computer search, as well as to abstract additional information. This has proved to be either not feasible or difficult when working with some other databases, in which original records were accessed in only 50% of the cases [22]. To date, studies performed with the GPRD in which medical records were requested have resulted in response rates well over 80%, and in many 90% or above [23]. Another unique additional feature of the GPRD is the possibility of sending the GP project specific questionnaires requesting information that is usually not recorded in the computer files. In some instances, questionnaires have also been sent to patients through their GPs, once consent was obtained both from GPs and patients. Due to the excellent collaboration of the participating GPs, around 80% of medical records are received within three months of the initial request date. As previously mentioned, all computer

and paper-based information is anonymized before being sent to researchers.

Areas for improvement

Additional computerized information At least in the area of pharmacoepidemiology, the key data for studies are demographic information, outpatient prescriptions and hospital-based diagnoses. However, in this and other research areas a number of other variables would be welcome, such as smoking habit, weight, height, life style (diet, exercise), socioeconomic and marital status. Some of these are already being recorded in the GPRD, although not yet routinely. Currently, data on smoking, weight and height are available for over 70% of the population. On the other hand, socioeconomic status information is not recorded at all. However, socio-economic scores exist at the practive level, and could be used with the practice instead of the patient as the unit of analysis. A limitation in reproductive epidemiology is the relatively low recording of date of conception, and weight and length at birth. Also, impacting specific areas of research are low recording levels of data such as: date of menarche and menopause, medical family history, and historical information on surgical interventions and chronic conditions. Other useful information would be recording data on over-the-counter medication (by asking the patient at each visit about over-the-counter drug use), in-hospital drug use, and other health care treatments delivered outside the GP practice (e.g. chemotherapy, PUVA). Finally, direct economic information on health care resource utilization is not present in the GPRD.

Linkage to other health care databases Linkage to other existing health care automated databases would be welcome to facilitate follow-up and diagnostic validation processes. One of the most desirable would be a linkage to hospital databases containing information on discharge diagnoses and procedures performed. Other useful linkages would be to cancer registries, congenital malformation reporting systems, and laboratory test results databases. In principle, these links could be arranged.

Additional research units The complexities of observational data and in particular GPRD data requires an extended period of learning before embarking on studies using the GPRD as the primary source of information. Experience with the GPRD is still limited and restricted to a handful of research units around the world. Also, input from these researchers could help to improve certain aspects of future data collection, such as those mentioned in point one above.

Applications of the GPRD in pharmacoepidemiology

The ultimate goal of pharmacoepidemiology is to provide reliable data to expand the knowledge about use and effects of drugs in the general population. Eventually, these data should contribute to evidence-based decision making by regulatory authorities and industry. The areas in which the GPRD, as well as all other already mentioned databases, can support pharmacoepidemiology span the whole life cycle of a drug. Four main areas of application can be identified: 1—to document baseline information in therapeutic areas, 2—to improve safety surveillance activities, 3—to assess the effectiveness of drugs, 4—to improve the balance of benefits and risks, and 5—to perform economic evaluation.

1 To document baseline information in disease areas

The GPRD can provide detailed data about the prevalence and incidence of diseases, distribution of risk and preventive factors, and patterns of drug utilization. In addition, observational data from the general population are vital for adequately assessing unmet medical needs, and planning areas where support is needed to improve public health conditions (basic research, clinical development, health care utilization studies, etc.).

2 To complement drug safety surveillance activities

During clinical trials, specific patient populations are exposed to investigational drugs. By providing background data about the characteristics of these populations (age and sex distribution, concomitant diseases and mortality experience), data from the GPRD can be used for a systematic and timely interpretation of adverse events occurring during clinical trials. After the drug reaches the market, spontaneous surveillance systems monitor, on an ongoing basis, the safety of drugs in the final target population as used in real life setting and over extended periods of time. Quite often, these systems generate so called 'safety signals'. Most of these signals can be quantified through pharmacoepidemiological studies using the GPRD in a timely fashion, which allow the researchers to compare the risk associated with various medications in one therapeutic area. Finally, subpopulations at an especially high (or low) risk can also be identified with these studies.

3 To assess the effectiveness of drugs

It is well accepted that the clinical randomized trial is the gold standard to assess the efficacy of drugs. However, there are certain instances where practical or ethical considerations prevent some clinical trials from being performed. During clinical trials, the benefits of a drug are evaluated in an ideal study setting (efficacy). Yet, the benefits in the real life setting should be documented once the drug is marketed (effectiveness) so that the clinical impact can be confirmed in the final target population. Also, sometimes new benefits of a drug can be identified and evaluated with automated data. Since real life data are rarely available on large sets of patients, the GPRD offers the opportunity to study the clinical impact of drugs based on general population data.

4 To improve the balance of benefits and risks of drugs

Epidemiologic studies based on the GPRD allow for the quantitative assessment of the benefits and risks of drugs to objectively estimate the overall impact of a drug in a real life setting.

5 To perform economic evaluation

Health care resource utilization data (outpatient visits, hospitalizations, laboratory tests, etc), as well as quality of life data, can be obtained from the GPRD, and serve as an input to pharmacoeconomic studies.

Pharmacoepidemiological studies performed using the GPRD

Appendix 1 lists a compilation of over fifty studies that have been published to date using the GPRD. The majority are in the drug safety field, covering many therapeutic areas such as nonsteroidal anti-inflammatory drugs, hormone replacement therapy, anti-infective agents, oral contraceptives, antihypertensive drugs, acid suppressing drugs, antidepressants, anticonvulsants, and diseases such as asthma, and diabetes. The clinical outcomes of these studies were among others, liver disorders, upper gastrointestinal bleeding and perforation, metabolic and endocrine disorders, seizures, suicide, blood dyscrasias, severe cutaneous adverse reactions, ocular disorders, myocardial infarction, neoplasia, sudden unexplained death, congenital malformations, venous thromboembolism, renal disorders, and bacterial infections. The database has been less frequently used for drug utilization and natural history of disease studies, pharmacoeconomic and health care utilization research. However, a few studies are available in these areas: resources used by schizophrenic patients, evaluation of prevention strategies in the general practice setting, resources needed for the care of patients with eating disorders, use of influenza vaccines, and natural history and drug utilization in asthma, and diabetes mellitus.

We will now briefly review some of the studies performed with the GPRD in the drug safety area that have had a prominent scientific and public health impact. We have chosen three studies; one that quantified the risk of acute hepatic injury in patients using the combination of amoxycillin with clavulanic acid, another one that compared the risk of developing cancer in users of different antihypertensive agents, and lastly a study that evaluated the risk of deep venous thromboembolism associated with oral contraceptives.

Several studies have been performed with the GPRD on the epidemiology of drug-induced liver injury [22]. Among antibiotics incriminated as hepatotoxic, use of the combination of amoxycillin and clavulanic acid has been the source of numerous case reports since the late 1980s. A large cohort study including over 90 000 users of the combination of amoxycillin and clavulanic acid, and 360 000 users of amoxycillin alone was identified with the GPRD, and followed for a two year period [24]. The objective of the study was to quantify and compare the risk of acute liver injury among users of these two antibiotics. After review of the original medical records, 35 cases met all the case definition criteria. The absolute risks of acute liver injury associated with the combination of amoxycillin and clavulanic acid, and amoxycillin alone were 1.7 and 0.3 per 10 000 prescriptions, respectively. There was a six-fold increase in risk in users of the combination vs users of amoxycillin alone. The data also made it possible to characterize the groups at highest risk, namely elderly patients receiving more than one course of amoxycillin and clavulanic acid combination therapy, whose risk of developing acute liver injury was greater than 1 per 1000. The clinical features of liver injury could be evaluated in detail based on the information from the medical records. This showed that the liver injury was predominantly cholestatic, and occasionally presented after the end of the combination therapy, confirming earlier individual case reports. Data from this study formed part of the evidence for revised conditions of use of the combination of amoxycillin and clavulanic acid in the U.K, and abroad [25].

An association was recently reported between the use of calcium-channel blockers (CCBs) and an increased risk of cancer overall. Using the GPRD resource, a study was conducted to assess whether cancer was associated with CCB use [26]. The source cohort was restricted to hypertensive patients using β-adrenoceptor blockers only, inhibitors of angiotensin-converting enzyme (ACE) only, or CCBs only. A nested case-control analysis was performed within this cohort. A total of 446 cases of cancer and 1750 controls were analyzed. After adjustment for smoking, body-mass index, change of antihypertensive medication, duration of hypertension, and diuretic use, the odds ratio estimates for all cancers combined were 1.3 (95% CI 1.0–1.6) for CCBs and 0.8 (95% CI 0.6–1.2) for ACE inhibitors, relative to β-adrenoceptor blockers. The corresponding odds ratio among patients older than 70 years was 1.2. No duration effect was found among users of CCBs, and a small dose effect was observed. Sub-group analyses by specific cancers did not show an increased risk for any particular location associated with use of CCBs. The authors concluded that no evidence of a material increase in the risk of any cancer or of any particular cancers was found associated with use of calcium-channel blockers, relative to use of β-adrenoceptor blockers. Subsequently, a second study also failed to demonstrate an excess risk among users of CCBs [27]. However, additional research is still needed to resolve the controversy.

The association between serious cardiovascular illness and use of different types of combined oral contraceptives (OCs) was examined in a large cohort study with a nested case-control analysis using the GPRD [28]. The study included over 300 000 otherwise healthy women who were current users of such preparations between 1991 and 1994. Since third generation oral contraceptives had been recently associated with an increased risk of such events, three combinations were evaluated, defined by the combined progestagen: levonorgestrel, desogestrel or gestodene. Overall cardiovascular mortality rates, and incidence rates of non fatal venous thromboembolism (VTE) per 100 000 woman-years of exposure were estimated for each group of users (mortality rates: 4.3, 1.5, and 4.8 respectively; VTE rates: 16.1, 29.3, and 28.1 respectively). The authors concluded that the risk of idiopathic cardiovascular death was low for all three preparations and that there was no large difference in risks between them. For VTE, there was a two-fold increase in risk among women using desogestrel or gestodene containing OCs when compared with levonorgestrel containing OCs, the risk being higher during the first six months of use. The excess risk of nonfatal VTE associated with third generation combined OCs compared

with levonorgestrel was estimated to be 16 per 100 000 woman-years. This study was performed rapidly because the results of two large field based studies, that had been ongoing for several years were causing concern to health authorities (the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception Study, and the Transnational Study on Oral Contraceptives and the Health of Young Women). Using the GPRD, the authors were able to perform a third study with large cohorts of users of the target treatments in less than 6 months. Recently, the GPRD was also used to evaluate the association of VTE and hormone replacement therapy among postmenopausal women [29].

Conclusion

In the recent history of pharmacoepidemiological research in Europe, the UK General Practice Research Database is the single largest source of published studies. GPRD data have been used extensively in the area of drug safety epidemiology, contributing on several occasions to decision making by regulatory authorities and industry. However, there are still some areas where the GPRD has been underused such as drug utilization, natural history of disease, pharmacoeconomics and health care utilization research.

Numerous studies have documented the completeness and high quality of the information recorded in the GPRD, as well as the excellent access to original medical records and collaboration of general practitioners. Welcome improvements would be the recording of additional information on life style habits and linkage to other medical databases.

The General Practice Research Database has proved that valuable data can be collected in a general practice setting. The potential of this rich computerized database has not yet been fully exploited. Hopefully, the coming years will witness new projects and expanding applications of this database. This experience should serve as a stimulus to efforts to generate similar population-based data in other countries.

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Appendix 1

Published manuscripts

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