Drug Utilization Studies

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Drug utilization studies aim to evaluate factors related to the prescribing, dispensing, administering and taking of medication, and its associated events (either beneficial or adverse).

Since the early 1960's the interest in Drug Utilization Studies has been increasing, first with market-only purposes, then for evaluating the quality of medical prescription and comparing patterns of use of specific drugs.

Presently drug utilization studies are an evolving area. Their scope is to evaluate the present state and future trends of drug usage, to estimate crudely disease prevalence, drug expenditures, appropriateness of prescriptions and adherence to evidence-based recommendations.

The increasing importance of drug utilization studies as a valuable investigation resource in pharmacoepidemiology has been bridging it with other health related areas, such as public health, pharmacovigilance, pharmacoeconomics, eco-pharmacovigilance or pharmacogenetics.

Key-words: epidemiology; pharmacology; pharmacoepidemiology; drug utilization.

The World Health Organization (WHO) addressed drug utilization as the marketing, distribution, prescription and use of drugs in a society, considering its consequences, either medical, social, and economic (1). Studies on the process of drug utilization focus on the factors related to the prescribing, dispensing, administering, and taking of medication, and its associated events, covering the medical and non-medical determinants of drug utilization, the effects of drug utilization, as well as studies of how drug utilization relates to the effects of drug use, beneficial or adverse (2-4). The therapeutic practice is expected to be primarily based on evidence provided by pre marketing clinical trials, but complementary data from post marketing period are needed to provide an adequate basis for improving drug therapy (5).

The interest in drug utilization studies began on both sides of the Atlantic in the early 1960s (3), and is still increasing (6,7). The first investigations (5,8,9) were conducted mostly for marketing purposes and data were not widely available for use by academic researchers or health authorities. The boost in the marketing of new drugs, the wide variations in the pattern of drug prescribing and consumption, the growing concern about the delayed adverse effects, and the increasing concerns regarding the cost of drugs, as reflected in the increase of both the sales and the volume of prescriptions all contributed to the increasing importance of drug utilization studies (10-13).

In the United States drug utilization research has been primarily developed at an institutional level or as part of as local health programs (3). Initially a great emphasis was placed on the study of the quality of physician prescribing habits, in particular with respect to antibiotics, in both hospital and outpatient settings (8,9,14). In Europe, the Scandinavian countries, Scotland, and Northern Ireland (9,15,16) pioneered the research at the national and international levels. The European drug utilization studies have been predominantly quantitative, describing and comparing patterns of use of specific groups of drugs according to geographic regions and time, showing wide variations in the utilization of drugs pertaining to several pharmaceutical classes (*e.g.*: anti-diabetics (15), psychotropics, nonsteroidal anti-inflammatory drugs [NSAIDS] (17), antihypertensive drugs, antibiotic drugs (12), and lipid-lowering drugs (18)).

SCOPE OF DRUG UTILIZATION STUDIES

Drug utilization studies may include descriptive epidemiological approaches to the study of drug utilization, but also the assessment of how drug utilization relates to the effects of drug use, beneficial or adverse.

The research in this field aims to analyse the present state and the developmental trends, of drug usage at various levels of the health care system, whether national, regional, local or institutional. Drug utilization studies may evaluate drug use at a population level, according to age, sex, social class, morbidity, among other characteristics. These studies are useful to provide denominators to cal-

culate rates of reported adverse drug reactions, to monitor the utilization of drugs from therapeutic categories where particular problems can be anticipated (*e.g.*, narcotic analgesics, hypnotics and sedatives, and other psychotropic drugs), to monitor the effects of informational and regulatory activities (*e.g.*, adverse events alerts, monitoring urgent safety restrictions). Drug utilization data may me used to produce crude estimates of disease prevalence (*e.g.*, cardiovascular disease (19), antidiabetic drugs (20)), to plan drug importation, production, and distribution, and to estimate drug expenditures.

The characterization of drug utilization may be extended linking prescription data to the reasons for the drug prescribing. They include the concept of appropriateness (3,8,9,14) that must be assessed relative to indication for treatment, concomitant diseases (that might contraindicate or interfere with chosen therapy) and the use of other drugs (interactions). Therefore they can document the extent of inappropriate prescribing of drugs (*e.g.* antibiotics, NSAIDs) and even the associated adverse clinical, ecological, and economic consequences (8,9,21,22). Moreover, they can also explore the percentage of drugs that adhere to the evidence-based recommendations in place for its indications (23,24).

DATA SOURCES

A considerable amount of data on drug usage is available as part of databases with administrative, commercial or clinical purposes, and specific investigations may be conducted to collect different types of information, qualitatively and quantitatively, or referring to a particular population.

Databases currently available for purposes of drug utilization studies may be classified as non-diagnosis-linked or diagnosis-linked (3). While the latter consider drug utilization linked to its indications and outcomes (e.g. treatment of peptic ulcer (25), trends in prescribing for heart failure (26)), the former concerns only about describing drug consumption in a population (*e.g.* use of antimicrobial drugs (22), statin consumption (18)).

Most of currently available data sources lack information on morbidity and are mostly used for generating drug statistics and descriptive studies of patterns of drug consumption. Some collect data in the form of drug sales (*e.g.*, The Portuguese National Authority for Medicines and Health Products (INFARMED), the Danish Medicines Agency, the National Agency for Medicines and Social Insurance in Finland, the Norwegian Institute of Public Health, the National Corporation of Pharmacies in Sweden,), drug movement at various levels of the drug distribution channel (*e.g*, IMS-Health [www.imshealth. com]), pharmaceutical or medical billing data or all prescriptions dispensed (Prescription Pricing Authority in the UK, Spain's Drug Data Bank, Medicaid Management Information System). However, since most statistics on drug consumption were compiled for administrative or commercial reasons, the data are usually expressed in terms of cost or volume of sales in units or weight that, although useful for measuring or comparing the economic impact of drug use, does not provide information on the amount of drug exposure in the population. Tablet sizes vary, making it difficult to translate weight into even the number of tables. Prescription sizes also vary, so it is difficult to translate number of tablets into the number of exposed patients (3). The WHO Drug Collaborating Centre for Drug Statistics, intend the use of the defined daily dose (DDD) as a technical unit of consumption to be employed in these type of studies (27).

The information on sales available through pharmacy records is the measure most frequently used in drug utilization studies (16,18,20). They provide detailed information on the drugs themselves although data on the consumer is usually very limited. This could be improved if a patient is allowed to purchase drugs at only one designated pharmacy, as is the case of the Netherlands, where reimbursement regulations require accurate recording of pharmacy data (28). But even in this situation, information such as the indication for use or extent to which patients actually consume the drugs will remain largely unknown and it should be noted that all these units represent approximate estimates of true consumption (3). The County of Jämtland Project (Sweden) is an example of longitudinal patient-specific studies of drug utilization (16,29,30). All drug prescriptions dispensed to 14% of the Jämtland population (approximately 17 000) have been continuously monitored since 1970. The recorded information includes the patient's unique identity number; name, dosage, quantity, and price of the drug; date of dispensing; dispensing pharmacy; and prescribing physician. Information relating to morbidity (diagnoses), however, is missing.

The Odense Pharmacoepidemiologic Database (OPED) and the pharmacoepidemiology prescription database of the County of North Jutland are two similar databases that include about half a million inhabitants in Denmark (31). These databases contain all dispensed prescriptions since the early 1990s. The following information is captured for each prescription: a unique person identifier, the date of dispensing, identification of the dispensed product, the pharmacy, and the prescriber. The databases do not include information on over-the-counter medications (laxatives, analgesics, ibuprofen, antihistamines, antitussives, and certain antacids) and non-subsidized drugs (oral contraceptives, hypnotics, and sedatives). They have been used for a number of population-based pharmacoepidemiologic surveys such as the use of the new antidepressants (13), inappropriate use of inhaled steroids in asthma treatment (32), inappropriate use of sumatriptan (33) and low use of long-term hormone replacement therapy (34).

The Community of Tierp Project is run by the Center for Primary Care Research, University of Upsalla, Sweden. Prescription and morbidity data are routinely collected from all pharmacies and the health center within the

community for all residents since 1972. The Swedish prescribed Drug register is a new register that contains data on all dispensed prescriptions for the entire Swedish population (about 9 million inhabitants) linking to the use of a unique personal identification number (7). The register does not include data on over-the-counter drugs, herbal drugs, drugs used in hospitals or from drugs storerooms sometimes used in nursing homes. It has information about individual's age, sex and dispensed drugs (amount of drug, date of redemption and dosage, *i.e.* from the prescription written by the prescriber).

The Portuguese National Pharmacy Association (ANF) has also been developing an interesting work. It has created since 1994 a centre for pharmacoepidemiology studies (CEFAR) and a database containing information on medicine consumption, based on dispensing data information from the Portuguese pharmacies. It has been conducting several drug utilization studies with a number of published work addressing different drug utilization issues such as self-medication (35,36) and antiasmaticals usage (37).

Data from general practiners (GP) records of prescriptions can be more informative about the indication for drugs prescribed, diagnoses and other health-related data, although these records are not always consistently completed (28). The National Disease of Therapeutic Index (NDTI), by IMS America, is an ongoing study of physician prescribing which is conducted mainly for use by pharmaceutical companies in their marketing activities (38). This study employs a rotating sample of office-based physicians who record all patient encounters and corresponding «drug mentions» for two-day periods, four times a year. A special prescription form is used to collect information on the drug (specific product, dosage form, new versus continuing therapy), patient characteristics (sex), prescriber (speciality, location, region), type of consultation (first versus subsequent), concomitant drugs and diagnoses, and the desired pharmacological action. Data has been made available to Academic Researchers and the US Food and Drug Administration (11). Although useful for studies of prescribing, longitudinal patient-specific studies are not possible with this database.

The Integrated Primary Care Information (IPIC) database, established at Erasmus University in The Netherlands, consists on the computer-based patient records of 150 general practiners. To date the database has accumulated data on approximately 500 000 patients. This database has been used to study preventive strategies in patients receiving NSAIDS (39) and trends in primary care prescribing for heart failure (26).

The Tayside Medicines Monitoring Unit (MEMO) and the General Practice Research Database (GPRD), in the United Kingdom, are databases developed primarily for drug safety studies, but have also been used to study drug utilization (40). GPRD exists since 1987, and is still growing in the number of practiners contributing data from over 460 general practiners, covering about 5.5% of the population of UK (3.5 million currently active research quality patients) being today the most published

database (41).

In Portugal, the National Observatory of Health (ONSA) analyses data related to health status and its determinants among the Portuguese residing population (42). It has a primary care surveillance network including 150 General Practiners across the country and has some published drug utilization studies regarding use of several therapeutic classes such as antibacterials (43), antiepileptics and antidepressives (44,45) and antacids (25). It has also an observational instrument created with the purpose of obtaining data and indicators on health with the help of a sample of Portuguese families with land-line telephones ("ECOS").

Data on drug utilization may be obtained directly from the population through Health surveys, including national surveys such as Statistics Canada's National Population Health Survey, or the Portuguese National Health Survey (also from the National Observatory of Health), or smaller surveys conducted in specific settings such as among university students (46), female population (47) or elderly outpatients (48). Such studies provide information on drug use from consumers themselves (49), and are a source of data on many other health-related issues (28).

INSTRUMENTS FOR DATA COLLECTION ON DRUG UTILIZATION

Patient files and computer registries are widely used as instruments for collecting information on drug utilization. Home inventories are also used and considered by some authors as the best method of obtaining accurate and complete drug use data (19,50,51). In this scenario, an interviewer visits the home of the respondent and lists all the drugs in the medicine cabinet. Questionnaires, however, are one of the easiest tools for data collection on drug utilization and the most widely used in population surveys.

Self-reported data in epidemiological studies obtained through questionnaires is commonly used as a source of drug exposure information (52). Data collected by self-report is, however, subject to recall inaccuracy (50,53-55). In some questionnaire-based studies only a limited number of drug categories were evaluated (53-55). In others, the completeness and quality of reference sources were debatable (56,57). In several studies questionnaire information was compared with pharmacy records (53,54), which are a reliable source of drug exposure, with an acceptable degree of agreement (28,51,52,58,59).

Despite being accurate, carefully constructed questionnaires can be subject to recall bias due to its characteristics, and noncompliance can also influence the reliability. Furthermore, questionnaire design also influences recall and may lead to different estimates on drug exposure (50,52,53,55).

Drug utilization data collected through questionnaires is commonly used in epidemiological studies but variations in questionnaire structure may affect recall. Therefore, in addition to a careful design of the data collection instru-

ments, the characteristics of the questionnaires used to obtain information on medicines need to be taken into account in the interpretation of results from studies quantifying drug utilization by self-report.

FUTURE PERSPECTIVES

The study of drug utilization is an evolving field. The use of large computerized databases that allow the linkage of drug utilization data to diagnosis, albeit subject to some inherent limitations, is contributing to expand this area of study.

Drug utilization studies have been having an increasing importance in pharmacoepidemiology by means of bridging more closely to other areas:

Public health

From a public health perspective, the differences observed in national and international patterns of drug utilization require much further study. Many strategies aimed at modifying prescribing behaviours have been proposed and adopted. Several studies have demonstrated the efficacy of face-to-face methods in improving drug prescribing by identifying physicians who were prescribing drugs assessed as inappropriate and targeting for educational or information activities (60-62).

However, drug utilization review programs as well as definition to what degree and which determinants of inappropriate prescribing are susceptible to modification and what might be an appropriate mix of interventions to achieve optimal impact merit further rigorous study.

Pharmacovigilance

Some of the actual existing databases have been developed primarily for drug safety studies (Tayside Medicines Monitoring Unit (MEMO) and the General Practice Research Database (GPRD) in the United Kingdom) (40). Pharmacovigilance plans require extend safety knowledge, in order to investigate potential drug-drug interactions and signal detection of adverse drug reactions. Drug utilization data can be used to perform screening for patients who may be at increased risk for drug-induced illnesses, often by use of concomitant drugs, abuse or overuse of drugs.

New registers offer countless possibilities for studying drug use among different groups of the society, but there is still a lot to achieve (7).

It is also important to evaluate the paediatric population, since many medicines prescribed for children are given «off-label» and surveillance of natural non-registered products, such as herbal medicines in the general population is also needed.

Pharmacoeconomics

Drug utilization reviews can be used for the improvement of medical care and cost-containment, and are useful for measuring or comparing the economic impact of drug use in the population. By identifying adherence to guidelines in the current use of medicines, it is possible to reduce drugs expenditure and improve the allocation of the limited resources available, when the chosen drugs are not usually the most cost-effective.

Eco Pharmacovigilance

Pharmaceuticals are environnement polluants. It is important to observe the differences in national and international patterns of drug utilization in order to address and minimize the environmental impact of pharmaceuticals whilst continuing to deliver patient benefit.

Pharmacogenetics

Trying to assess genetic mechanisms related to drug safety issues is also a challenge for drug utilization studies, while comparing consumers' characteristics and linking it to the benefit and risk of drugs.

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