

Chapter 10. Drug Utilization

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I. INTRODUCTORY REMARKS

WHAT IS DRUG UTILIZATION RESEARCH AND WHY IS IT NEEDED

I.1. Definitions

Drug utilization research was defined by WHO in 1977 as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”. Since then, a number of other terms have come into use and it is important to understand the interrelationships of the different domains. **Epidemiology** is defined as “the study of the distribution and determinants of health-related states and events in the population, and the application of this study to control of health problems”. **Pharmacoepidemiology** applies epidemiological methods to studies of the clinical use of drugs in populations. A suitable definition of pharmacoepidemiology is: *The study of the use and effects/side effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes.*

Pharmacosurveillance and **pharmacovigilance** are terms used to refer to the monitoring of drug safety such as spontaneous adverse effect reporting systems, case-control and cohort studies.

Pharmacoepidemiology may be drug-oriented, emphasizing the safety and effectiveness of individual drugs or groups of drugs, or utilization-oriented aiming to improve the quality of drug therapy through pedagogic intervention. Drug utilization research may also be divided into descriptive and analytical studies. The emphasis of the former has been to describe patterns of drug utilization and to identify problems deserving more detailed studies. Analytical studies try to 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. Sophisticated utilization-oriented pharmacoepidemiology may focus on the drug (e.g., dose-effect and concentration-effect relationships), the prescriber (e.g., quality indices of the prescription), or the patient (e.g., selection of drug and dose vs. kidney function, drug metabolic phenotype/genotype, age, etc).

Drug utilization research is thus an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure. In common use, the distinction between these two terms has become less sharp, and they are sometimes used interchangeably. However, while drug utilization studies often employ various sources of information focusing on drugs, e.g., aggregate data from wholesale and prescription registers, the term epidemiology implies defined populations and that drug use can be expressed in terms of incidence and prevalence.

Drug utilization research and pharmacoepidemiology may provide insights into the following aspects of drug use and drug prescribing:

Pattern of use: extent and profiles of drug use and trends in drug use and costs over time.

Quality of use: audits comparing actual use to national and regional prescription guidelines or local drug formularies.¹ Quality indices of drug use may include the choice of drug (compliance to recommended assortment), drug cost (compliance to budgetary recommendations), drug dosage (awareness of inter-individual variations in dose requirements and age dependence), drug interaction

¹ An audit in drug use was defined by Crooks (1979) as an examination of the way in which drugs are used in clinical practice carried out at intervals frequent enough to maintain a generally accepted standard of prescribing.

awareness, ADR awareness, proportion of patients being aware of/unaware of the cost/benefit of the treatment, etc.

Determinants of use: user characteristics (e.g. socio-demographic parameters, attitude towards drugs), prescriber characteristics (e.g. specialty, education and factors influencing therapeutic decisions), and drug characteristics (e.g. therapeutic properties, affordability)

Outcomes of use: health outcomes (benefits and adverse effects) and economic consequences.

Pharmacoepidemiology initially focused on the safety of individual drug products (pharmacovigilance), but now also includes studies of their beneficial effects. The driving force behind this development was a growing awareness that health outcomes of drug use in the rigorous setting of randomized clinical trials is not necessarily the same as health outcome of drug use in everyday practice. The clinical trials that are needed to obtain marketing authorization for new drugs involve limited samples of carefully selected patients, who are treated and followed-up for a relatively short period of time in strictly controlled conditions. As a result, such trials do not provide an accurate reflection of how drug use will impact health outcomes in everyday practice under everyday circumstances. Pharmacoepidemiological studies often make useful contributions to our knowledge about effectiveness and safety, because they assess drug effects in large, heterogeneous patient populations over longer periods.

Drug utilization research also provides insight into the efficiency of drug use, i.e. whether a certain drug therapy provides value for money. Drug utilization research can thus help to set priorities for the rational allocation of health care budgets.

I.2. Why drug utilization research?

The principal aim of drug utilization research is to facilitate rational use of drugs in populations. For the individual patient rational use of a drug implies the prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and at an affordable price. Without knowledge on how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use and to suggest measures to change prescribing habits for the better. Information on the past performance of prescribers is the linchpin of any auditing system.

Drug utilization research in itself does not necessarily provide answers, but it contributes to rational drug use in three important ways:

I.2.A. Description of drug use patterns

Drug utilization research will increase our understanding of how drugs are being used by:

- a. Making estimates of the numbers of patients exposed to drugs within a given time period. Such estimates may either refer to all drug users, regardless of when they started to use the drug (**prevalence**), or focus on patients who started to use the drug within the selected period (**incidence**).
- b. Describing the extent of use at a certain moment and/or in a certain area (e.g. country, region, community, hospital). Such descriptions are most meaningful when they are part of a continuous evaluation system, i.e. when the patterns are followed over time and trends in drug use can be described.
- c. Estimating (e.g. on the basis of epidemiological data on a disease) to what extent drugs are properly used, overused, or underused.
- d. Describing the pattern or profile of drug use - assessing which alternative drugs are being used for particular conditions and to what extent.

- e. Comparing observed patterns of drug use with current recommendations or guidelines for the treatment of a certain disease.
- f. Applying quality indicators to drug utilization patterns. An example is the so-called DU90% (drug utilization 90%), a further development of the "Top-10" list. The DU90% segment reflects the number of drugs that account for 90% of drug prescriptions and adherence to local or national prescription guidelines in this segment. This general indicator can be applied at different levels (individual prescriber, group of prescribers, hospitals, region, county, etc.) to get a rough estimate of the quality of prescribing.
- g. Feeding back drug utilization data to prescribers. This is particularly useful when the individual's drug prescribing can be compared with some form of "gold standard" or best practice, and with the average prescriptions in the country, the region, or the area.
- h. Relating the number of case reports about a drug problem or adverse effects to the number of patients exposed in order to assess the potential magnitude of the problem. If it is possible to detect that the reaction is more common in a certain age group, in certain conditions or at a special dose level, improving the information on proper use such as indications, contraindications and appropriate dosages may be sufficient to assure a safer use. Thereby withdrawal of the drug from the market may be avoided.

I.2.B. Early signals of irrational use of drugs

Drug utilization research may generate hypotheses that set the agenda for further investigations by:

- a. Comparing drug utilization patterns and costs between different regions or time periods. Hypotheses can be generated to form the basis for investigations of the reasons for, and health implications of, the differences found. Geographical differences and changes over time in drug use may have medical, social and economic implications both for the individual patient and for society, and are thus important to identify, explain and sometimes correct.
- b. Comparing observed patterns of drug use with current recommendations/guidelines for the treatment of a certain disease. Hypotheses can then be generated about whether discrepancies represent less than optimal practice, whether pedagogic interventions (education) are required, or whether the guidelines need to be reviewed in the light of actual practice. These considerations should include both underuse and overuse of drugs.

I.2.C. Interventions to improve drug use – follow-up

Drug utilization research may enable us to assess whether interventions undertaken to improve drug use have had the desired impact by:

- a. Monitoring and evaluating the effects of measures taken to improve undesirable patterns of drug use (regional or local formularies, information campaigns, regulatory policies, etc.)
- b. Following the impact of regulatory changes or changes in insurance or reimbursement systems. This also requires a broad survey, because the total cost to society may remain the same or may even increase, if other more expensive drugs are used as an alternative.
- c. Assessing to which extent promotional activities of the pharmaceutical industry and educational activities of the society impact on the patterns of drug use.

II. TYPES OF DRUG USE INFORMATION

Different types of drug use information are required depending on the problem being evaluated. These include information about the overall drug use, or use of drug groups, individual generic compounds or specific products. Often, information about the condition being treated, about the patient and about the

prescriber will be required. In addition, data on drug costs will be important in ensuring that drugs are used efficiently and economically. These types of drug information are described below.

II.1 Drug based information

The trends in total drug use may sometimes be useful to know, but more detailed information is usually required to answer clinically important questions. This may involve aggregation of drug use at various levels, and information on indications, doses and dosage regimens.

II.2. Problem or encounter-based information

Instead of asking how a particular group of drugs is used, one may well address the question how a particular problem (e.g. sore throat, hypertension, gastric ulcer, depression) is managed.

II.3. Patient information

Demographic and other information about the patient will often be useful. The age distribution of patients will sometimes be of critical importance, for example to assess the likelihood of severe adverse effects with NSAIDs, or whether the drug is being used in an age group different to that in which the clinical trials were performed. The co-morbidities of the patient group may be important in determining treatment choice and adverse effects. As an example in the management of hypertension, beta-blockers should be avoided in patients with asthma, and ACE inhibitors preferred in patients with heart failure.

Qualitative information such as knowledge, beliefs, and perceptions among patients and their attitudes to drugs will be important in some cases, for example in assessing patient pressures on doctors to prescribe antibiotics, or in designing consumer information/education programs.

II.4.Prescriber information

The prescriber is a critical point in determining drug use. Some sceptics even claim that doctors differ more than patients and that differences in drug prescribing often lack rational explanations. Dissecting the factors that determine prescribing behaviour is therefore often central to understanding how and why drugs are prescribed.

III. SOURCES OF DRUG UTILIZATION DATA

The drug use chain includes the processes of drug acquisition, storage, distribution, prescribing, patient compliance and review of outcome of treatment. Each of these events is an important aspect of drug utilization. Drug utilization data may be derived from quantitative or qualitative studies. Quantitative data may be used to describe the present state, and trends in drug prescribing and drug use at various levels of the health care system. Quantitative data are usually obtained from routinely collected data or from surveys. Qualitative studies assess the appropriateness of drug utilization and generally link prescribing data to reasons (indications) for prescribing. Such studies have been referred to as Drug Utilization Review or Drug Utilization Evaluation. The process is one of a “**therapeutic audit**” based on defined criteria and has the purpose of improving the quality of therapeutic care. There is an increasing interest in the evaluation of the economic impact of clinical care and medical technology. This has evolved into a discipline dedicated to the study of how pharmacotherapeutic methods influence resource utilization in health – **pharmacoeconomics**.

The increasing interest in efficient use of health care resources has resulted in the establishment of computer databases for studies on drug utilization. Some of the databases can generate statistics for

patterns of drug utilization and adverse drug reactions. Data may be in the form of drug sales, drug movement at various levels of the drug distribution chain, pharmaceutical and medical billing data or samples of prescriptions. Data may also be obtained from drug importers, wholesalers or local manufacturers.

Data from medical practices and health facilities may be used to measure specific aspects of health provision and drug use. Such data may be used to generate indicators that provide information on prescribing habits and aspects of patient care. These indicators can be used to determine where drug use problems exist, provide a mechanism for monitoring and supervision and motivate health care providers to follow established health care standards.

Prescription and dispensing data are useful for determining some of the quality indicators of drug use recommended by WHO. These include:

- a. Average number of drugs per prescription (encounter)
- b. Percentage of drugs prescribed by generic name
- c. Percentage of encounters with an antibiotic prescribed
- d. Percentage of encounters with an injection prescribed
- e. Percentage of drugs prescribed from essential drugs list or formulary
- f. Average drug cost per encounter

III.1 Drug use evaluation

Drug use evaluation is a system of ongoing, systematic, criteria-based drug evaluation that ensures the appropriate use of drugs. Drug use evaluation is sometimes referred to as drug utilization review. It is a method of obtaining information to identify problems of drug use. Properly developed, it not only provides a means of identifying drug use problems but also provides a means to correct the problem and thereby contributes to rational drug therapy.

Drug use evaluation can assess the actual process of medication administration or dispensing (appropriate indications, drug selection, dose, route of administration, duration of treatment, drug interactions) and also assess outcomes of treatment (cured disease conditions, decreased levels of a clinical parameter). The objectives of drug use evaluation include:

- a. Ensuring that drug therapy meets current standards of care
- b. Controlling drug cost
- c. Preventing medication related problems
- d. Evaluating the effectiveness of drug therapy
- e. Identification of areas of practice that require further education of practitioners

Identification of problems to be subjected to drug use evaluation may be obtained from any of the data from the practice setting section (prescription indicators, dispensing data, aggregate data). The main source of data for drug use evaluation is the patient records. An identifiable authoritative group, like the Drugs and Therapeutic Committee, usually carries out drug use reviews in the hospital or health facility. This group has the responsibility of drawing up the guidelines, criteria, indicators and thresholds for the evaluation. Drug use evaluation may be based on data collected prospectively (as drug is being dispensed or administered) or retrospectively (based on chart reviews or other data sources).

IV. DRUG CLASSIFICATION SYSTEMS

A drug classification system represents a common language for describing the drug assortment in a country or region and is a prerequisite for national and international comparisons of drug utilization

data, which have to be collected and aggregated in a uniform way. Access to standardised and validated information on drug use is essential to allow audits of patterns of drug utilization, to identify problems in drug use, to initiate educational or other interventions and to monitor the outcomes of the interventions. The main purpose of having an international standard is to be able to compare data between countries. A recent example is the international focus on creating comparable monitoring systems for cross-national antibacterial utilization patterns in the work against bacterial resistance.

IV.1 Different classification systems

Drugs can be classified in different ways: according to their mode of action, according to indications, or according to chemical structure. Each classification system will have its advantages and limitations and the usefulness will depend on the purpose, the setting used, and the user's knowledge of the methodology. Comparisons between countries may require a different classification system than a local comparison (e.g. between different wards in a hospital). Of the various systems proposed over the years, only two have survived to attain a dominant position in drug utilization research worldwide. These are the Anatomical Therapeutic Classification (AT) developed by the European Pharmaceutical Market Research Association (EPhMRA) and the Anatomical Therapeutic Chemical (ATC) classification developed by Norwegian researchers. These systems were originally based on the same main principles. In the EPhMRA system, drugs are classified in groups at three or four different levels. The ATC classification system is modified and extended from the EPhMRA system by the addition of a therapeutic/pharmacological/chemical subgroup as the fourth level and the chemical substance as the fifth level.

ATC is also the basis for the classification of adverse drug reactions used by the WHO Collaborating Centre for International Drug Monitoring in Uppsala (www.who-umc.org).

The main purpose of the ATC classification is as a tool for presenting drug utilization statistics and it is recommended by the WHO to be used in international comparisons. The EPhMRA classification system is used world wide by IMS (Intercontinental Medical Statistics) for providing marketing research statistics to the pharmaceutical industry. It should be emphasised that there are many technical differences between the EPhMRA classification and the ATC classification. Therefore, data prepared using the ATC classification cannot be directly compared with those obtained with the EPhMRA system. In 1996, WHO established the ATC/DDD system as an international standard in drug utilization studies.

IV.2. The ATC classification system

In the Anatomical Therapeutic Chemical classification system the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties.

Drugs are classified in groups at five different levels. The drugs are divided into fourteen main groups (1st level), with two therapeutic/pharmacological subgroups (2nd and 3rd levels). The 4th level is a therapeutic/pharmacological/chemical subgroup and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when this is considered to be more appropriate than therapeutic or chemical subgroups.

The complete classification of glibenclamide illustrates the structure of the code:

A	Alimentary tract and metabolism <i>(1st level, anatomical main group)</i>
A10	Drugs used in diabetes <i>(2nd level, therapeutic main group)</i>
A10B	Oral blood glucose lowering drugs <i>(3rd level, therapeutic/pharmacological subgroup)</i>
A10B B	Sulfonamides, urea derivatives <i>(4th level, chemical/therapeutic/pharmacological subgroup)</i>
A10B B01	Glibenclamide <i>(5th level, subgroup for chemical substance)</i>

Thus, in the ATC system all plain glibenclamide preparations are given the code A10B B01.

Alterations in the ATC classification are made when the main use of a drug has clearly changed, and when new groups are required to accommodate new substances or to achieve better specificity in the groupings.

In the ATC system drugs are separated into groups at five different levels (described above). By use of this classification system, statistics of drug utilization grouped at five different levels can be provided; from figures showing total drug use of all products classified e.g. in a main group (1st level), to figures for the different subgroups (2nd, 3rd and 4th level) and down to figures showing use of the separate substances.

The publication *Guidelines for ATC Classification and DDD Assignment* gives further and detailed information about the ATC classification. (WHO Collaborating Centre for Drug Statistics Methodology, 2003; www.whocc.no)

V. DRUG UTILIZATION METRICS AND THEIR APPLICATIONS

V.1. The concept of the defined daily dose (DDD)

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

The defined daily dose is a unit of measurement and does not necessarily agree with the recommended or prescribed daily dose (PDD). Doses for individual patients and patient groups will often differ from the DDD and have to be based on individual characteristics (e.g. age and weight) as well as pharmacokinetic and pharmacogenetic considerations.

The DDD is often a compromise based on a review of the available information about doses used in various countries. The DDD may even be a dose that is rarely prescribed, because it is an average of two or more commonly used dose sizes.

Drug utilization figures should preferably be presented as numbers of DDDs/1000 inhabitants/day or, when in-hospital drug use is considered, as DDDs per 100 bed days. For anti-infectives (or other drugs normally used in short periods), it is often considered most appropriate to present the figures as numbers of DDDs per inhabitant per year.

These terms are explained in the following:

V.1.A. DDDs/1000 inhabitants/day

Sales or prescription data presented in DDD/1000 inhabitants/day may provide a rough estimate of the proportion of the study population that may be treated daily with certain drugs. As an example, the figure 10 DDDs/1000 inhabitants/day indicates that 1 % of the population on average might get a certain drug or group of drugs every day. This estimate is most useful for chronically used drugs when there is good agreement between the average prescribed daily dose (see below) and the DDD. It may also be important to consider the size of the population used as a denominator. Usually the general utilization is calculated for the total population including all age groups. Some drug groups have very limited use among young people, with most users above the age of 45. To correct for utilization differences due to differing age structures between countries, simple age adjustments can be made by using the number of inhabitants in the relevant age group as a denominator.

V.1.B. DDDs per 100 bed days

This unit may be applied when in-hospital drug use is considered. As an example, 70 DDD/100 bed days of hypnotics provide an estimate of the therapeutic intensity and suggests that 70% of the in-patients might receive a DDD of a hypnotic every day. This unit is quite useful for benchmarking in hospitals.

V.1.C. DDDs per inhabitant per year

This term may give an estimate of the number of days for which each inhabitant is, on average, treated annually. For example, 5 DDDs/inhabitant/year indicates that the utilization is equivalent to the treatment of every inhabitant with a 5 days course during a certain year. Alternatively, if the standard treatment period is known, the total number of DDDs can be calculated as the number of treatment courses, and the number of treatment courses can then be related to the total population.

V.2. Prescribed daily dose/Consumed daily dose

The prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions. The PDD can be determined from prescription studies and medical- or pharmacy records. It is important to relate the PDD to the diagnosis for which the dosage is based. The PDD will give the average daily amount of a drug that is actually prescribed. When there is a substantial discrepancy between the PDD and the defined daily dose (DDD), it is important to take this into consideration when evaluating and interpreting drug utilization figures, particularly in terms of morbidity.

The PDD can vary according to both the illness treated and national therapeutic traditions. There are also substantial differences between PDDs in various countries. PDDs in Asian populations are often lower than in Caucasians. The fact that PDDs may differ from one country to another should always be considered in international comparisons.

It should be noted that the prescribed daily dose does not necessarily reflect actual drug utilization. Some prescribed medications are not dispensed, and the patient does not always take all the medications that are dispensed. Specially designed studies including patient interviews are required to measure actual drug intake at the patient level (i.e. consumed daily dose).

V.3. Volume

Common physical units (e.g. grams, kilos, litres), numbers of packages or tablets and numbers of prescriptions are also used for quantifying drug utilization. These units can be applied only when the use of one drug or of well-defined products is evaluated.