A Review of Drug Utilization Studies and Methodologies

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ABSTRACT

Drug utilization is defined by the World Health Organization (WHO) as the marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences. This article gives a concise overview of drug utilization studies. It describes the definition, history, purposes, types, process and methods used in drug utilization studies. The ultimate purposes of drug utilization studies are to contribute to the optimal quality of drug therapy by identifying, documenting and analyzing problems in drug utilization and monitoring the consequences of interventions. Different types of drug utilization studies can be conducted and various methods can be used. Special emphasis is placed in this review on consumption studies (volume, cost and the Defined Daily Dose (DDD) methodology). The study of drug utilization continues to evolve. The development of large computerized databases linking drug utilization to diagnoses and other lifestyle information has made drug utilization studies a powerful scientific tool for ensuring the rational and cost-effective use of drugs in society.

Keywords: Drug utilization, Consumption studies, Prescribing patterns, Defined Daily Dose (DDD), Pharmacoepidemiology.

INTRODUCTION

There are more effective drugs (medicines) today on the market than ever before. Patients are better educated, have greater expectations from health care, and frequently use multiple sources of health care. Yet, drugs are frequently not used to their full potential or according to the generally accepted criteria. All prescribing is not necessarily based on patient needs and all patient needs are not necessarily met with drug therapy. Consequently, there is as much concern about inappropriate and expensive prescribing, as about under-prescribing. The development of drug utilization as a research area made it possible to study drug prescribing and drug usage in a scientific and formal manner. The aim of this review is to give a concise overview of drug utilization studies, including the different methods that are used.

DEFINITION OF DRUG UTILIZATION

Drug utilization is defined as “the prescribing, dispensing, administering, and ingesting of drugs”\(^1\). The World Health Organization (WHO) expands on this definition by including outcome variables in their definition.\(^2\) Drug utilization is defined by the WHO as the “marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences."\(^1\)

A drug utilization study is therefore a study designed to describe-quantitatively and qualitatively-the population of users of a given drug (or class of drugs) and/or the conditions of use (for example, indications, duration of treatment, dosage, previous or associated treatments and compliance).\(^3\) Tognoni\(^1\) noted that if the emphasis of a study is on drug utilization, the point of observation is the act of prescribing the drug. Drug
utilization studies may be quantitative or qualitative. (4)
Quantitative data need to be obtained on the extent and
variability in usage and costs of drug therapy, from
which medical and social qualitative consequences can
be extrapolated. Drug utilization studies also provide the
base from which further qualitative research can be
conducted.

HISTORICAL DEVELOPMENT OF DRUG
UTILIZATION

The beginning of drug utilization studies can be
traced back to the early 1960s. (5) During a symposium
on drug toxicology organized by the WHO in Moscow
in 1964, serious consideration was first given to major
public studies of drug utilization. (5) Similar to many
other developments at the time, drug utilization had
been sparked off by the thalidomide disaster (5). People
came to the realization that if they had no idea of the
scale on which (and the manner in which) such
dangerous products had been employed, they were not
in a position to assess the frequency and location of the
risks. The Moscow meeting led to a study of drug
consumption in six European countries in the 1966 to
1967 period, which showed great differences in drug
use (5). This study was followed by a symposium
entitled, "The consumption of drugs" in Oslo in 1969,
which clearly confirmed that an internationally accepted
classification system was needed for presenting data on
drug consumption. Drug utilization studies were
originally a northern European project but have since
spread to all the parts of the world. It was initially
motivated by economic considerations but has become
one serving the interests of efficient, effective and safe
medicine (5).

The focus of drug utilization activities has gone
along different avenues on opposite sides of the Atlantic
Ocean. In North America, drug utilization studies
usually started at the individual patient level whether in
hospital or in an ambulatory care setting. Drug Regimen
Review (DRR) and Drug Utilization Review (DUR)
systems use as their focus the single patient or the
individual prescriber, depending on the purpose of the
study. DRR is used to assure that the optimal therapy is
selected for a patient, for example in the most
efficacious dosage form and schedule. It also considers
the health status of the patient, concurrent pathological
features, therapy, and other considerations such as
allergies, choice of dosage form and compliance factors.
DUR is used for similar purposes, but the emphasis is
different. DUR can also be used as a quality assurance
tool to examine the prescribing characteristics of
different medical practitioners. DUR thus makes it
possible to identify, for example, high-cost prescribers
or those using an extraordinary quantity or proportion of
certain products. Any deviations can then be further
studied and evaluated.

In Europe, and in Scandinavia in particular, the
approach had started with the sales records' strategy. (6)
In these studies, the quantity of drugs used by country,
county, or any other geographic area where data could
be collected separately were compared. This made it
possible to compare the sales of aspirin or any other
drug product on an area-by-area basis and divide the
sales by a per-person denominator. This method was
formalized with the creation of the Defined Daily Dose
(DDD) system as a means of estimating drug sales, and
via this scheme, serve as a proxy for drug consumption
or utilization.

LEVELS OF DRUG UTILIZATION

Drug utilization can be studied at various levels
depending on the purpose of the study and the facilities
and information available. Table (1) illustrates the four
basic levels at which drug utilization research can be
conducted, with their respective secondary levels. Each
study must be related to a specific time period (for
example, a year, a quarter, a month or a day) and to a
specific unit of the population. Furthermore, the data
used should be suitable for the type of research
undertaken, that is, whether for medical or
pharmaceutical purposes, or for administrative or
commercial purposes.
Table (1): Levels of cost or quantity parameters in drug utilization research (7)

<table>
<thead>
<tr>
<th>First level</th>
<th>Second level</th>
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<tbody>
<tr>
<td>Drug</td>
<td>All drugs</td>
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<td></td>
<td>Groups of drugs</td>
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<td>Single drugs/products</td>
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<td>Area/sources</td>
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<td>Region(s)</td>
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<td>Pharmacy/pharmacies</td>
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<td>Health insurance system(s)</td>
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<td>Hospitals/hospital wards/hospital beds</td>
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<td>Prescriber(s)</td>
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<td>Patient(s)</td>
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<td>Levels of therapy</td>
<td>Wholesale/overall pattern</td>
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<td></td>
<td>Prescriptions</td>
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<td></td>
<td>Patient compliance/non-compliance</td>
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<td></td>
<td>Pharmacokinetics/pharmacodynamics</td>
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<tr>
<td>Unit of measurement</td>
<td>Cost (overall cost or unit cost)</td>
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<td></td>
<td>Quantity (overall weight/volume or unit quantity)</td>
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</table>

A SYSTEMS VIEW OF DRUG UTILIZATION

Drug utilization has created a broad arena for the development of innovative approaches to improve drug use. However, the definition of drug utilization tends to create expectations that there could be a "gold standard" of drug utilization that can be met with the optimal information, education and behaviour of prescribers, pharmacists and patients. Although such an ideal may be feasible in a static environment, the coexistence of the evolving sciences of drug development, clinical pharmacology and pharmacoepidemiology, coupled with an equally dynamic and highly competitive pharmaceutical market, creates a major challenge to the achievement of this ideal. Thus, according to Jones(8), a systems view and consideration of some of the constraints to the achievement of ideal drug utilization are necessary.

In any setting, drug utilization can be viewed as an evolving management system applied to an underlying health care system. This view of drug utilization is illustrated in Figure (1). Each system typically consists of input, process and output components. The systems view begins with definitions of desired and realistic output (for example, a specified percentage of decreased costs, hospitalizations or drugs per patient), then of the available input (the health care system and data structure) and, finally, the process (the establishment of criteria, the application thereof, intervention strategies and finally evaluation). Furthermore, given a continuously changing health care and therapeutic environment, re-evaluation on a frequent basis is necessary.
There is thus an interrelationship between drug utilization research and the environment in which it is conducted. Therefore, it is not appropriate to view drug utilization by itself; rather, it must be seen as a process consisting of several steps (these steps are discussed later).

**PURPOSES OF APPLYING DRUG UTILIZATION REVIEW**

Drug utilization studies, depending on the setting and the underlying priorities, may be used for a variety of purposes. The purposes of any individual drug utilization study should be clarified in detail before the process is started. It can be used to:

- measure, for example, the effect of informational and regulatory efforts, and price policy;
- detect or identify problems and define areas for further investigation on the absolute and relative efficacy and safety of drug therapy;
- aid in the determination of benefit-risk and cost-effectiveness; and
- suggest overuse, under-use, or misuse of single drug compounds or therapeutic classes of drugs.

From a more macroscopic view, three broad purposes of DUR can be distinguished, namely:

- ** Improvement of the quality of care**
  
  Drug therapy is an integral part of high-quality medical care, embracing the concepts of both quality control and quality assurance. Quality control relates to process-oriented criteria that measure factors such as appropriateness of dose or duration of therapy. Quality assurance relates to measuring outcomes of therapy with drugs. This focus on enhanced quality as a primary goal is paramount in drug utilization research. Quality of care thus reflects appropriate, cost-effective, and medically necessary interventions that maximise the probability of a favourable health outcome.

- ** Containment of the cost of medical care**
  
  Drug utilization studies can examine costs by patient, provider, individual drug, or a combination of the three aspects. Although not necessarily the main objective of all drug utilization studies, the containment of medical care costs is receiving increasing interest. There is a natural tension among manufacturers who want to maintain profits and research operations, consumers who want the best possible health care, and providers who wish to limit costs without
harming their own financial position. It must also be taken into account that health care professionals are often not preoccupied with cost. In recent years, however, it became a reality that cost must be a factor in diagnostic and therapeutic decisions.

- Identification and control of fraud and abuse

Although not generally seen as forming part of the DUR process, it is possible to identify and attempt to control fraud and abuse when performing drug utilization studies since many aspects involved in fraud and abuse relate to the quality of care and cost issues.

TYPES OF DRUG UTILIZATION REVIEW

Three broad categories of DUR are recognized, namely retrospective studies, concurrent reviews, and prospective reviews\(^{(9)}\).

- Retrospective studies

A retrospective drug utilization study is an approved, systematic process that captures, reviews, analyses, and interprets aggregate medication use data within specific health care environments.\(^{(10)}\) Data are archival in nature, in other words collected and analyzed after the events of major interest (the prescription, dispensing, and use of drugs) have occurred. The specific health care environment influences retrospective drug utilization because the quality and quantity of the data determine the scope, nature, and application of the review. These studies have little impact on immediate patient care but rather serve to identify trends in prescribing practices that may lead to interventions aimed at enhancing prescribing behaviour. Their potential for preventing problems is limited, because the actual review may not take place for weeks after an error has been made or an inappropriate therapy has been administered. Retrospective studies are inexpensive, can be conducted rapidly and have easily accessible data.

- Concurrent reviews

Concurrent reviews are conducted simultaneously with the dispensing process. If a potential problem is discovered, the dispensing function stops until authorization is received to continue as before or to initiate a modification or dosage correction. Concurrent reviews thus prevent therapeutic misadventures. They are more expensive and time consuming than retrospective studies, but have the potential for much greater pay-offs in preventing problems. Concurrent reviews require a computer system or a well-organized manual drug profile system. Even so, unless the databases of the various pharmacies, that a patient patronizes, as well as the database of the hospitals or clinics are merged, the patient will not be optimally served. This is a serious and major flaw found in most concurrent programs.

- Prospective reviews

Prospective review is the option closest to the ideal and is more comprehensive than a concurrent review. Use of prospective review, based upon a complete drug and medical history obtained from an interview and from historical records, permits the practitioner to evaluate the patient's pre-existing therapy on a retrospective basis, and then to prevent interactions by disallowing certain drugs for a patient on the basis of a pre-existing review and by protocols already developed. The ideal set-up for prospective reviews is where the prescriber captures the prescription electronically. The database program then informs the prescriber why he or she should select another product, and guides him through a series of questions, after which some suggested products might be displayed on the screen. These reviews are only possible if computer equipment and the required software are available.

Retrospective and prospective DUR are not necessarily mutually exclusive. Their integration has the potential for the promotion of optimal prescribing practices. Retrospective DUR can detect new relationships and problems among medications and diseases. This information can then be programmed into a prospective DUR system to target patients who are at risk before drugs are dispensed.

DRUG UTILIZATION REVIEW PROCESS

Drug utilization review is the process by which the quality of drug prescribing is measured against explicitly determined criteria or standards. It is a dynamic process aimed firstly at rational prescribing and the consequent improvement of the quality of care, and secondly, at minimizing expenditures. These reviews have been an
important component of efforts to improve prescribing practices in both institutional and ambulatory care settings in various parts of the world. It provides the mechanism for developing standards, assessing current therapy, and implementing a specific intervention followed by reassessment of drug utilization.

The DUR process is a flexible and broadly applicable process that can be used to assess the quality and economy of drug prescribing, drug use by patients, and drug dispensing. The process is cyclic and dynamic, and can be divided into ten general steps\(^\text{(10)}\), namely:

- design the basic structure;
- seek approval;
- construct indicators and criteria;
- apply indicators and criteria to database;
- evaluate and analyze yield;
- establish prescribing patterns;
- establish intervention strategies;
- measure outcomes;
- reapply criteria to database; and
- revise indicators and criteria as needed.

**REVIEW OF METHODS USED IN DRUG UTILIZATION STUDIES**

The development of methodological tools for drug utilization studies started at the beginning of the 1970s\(^\text{(11)}\). Since then, various methods to study the utilization of drugs have been described in the literature. Some of these methods made it possible to compare international and interregional research, while other methods were more suitable for evaluation at the individual hospital, health centre or medical aid level. In order to measure drug use, it is important to have both a classification system and a unit of measurement. Furthermore, in order to study drug use over time, it is important to have a stable and consistent method which makes it possible to compare drug statistics both nationally and internationally. Unfortunately, not all drug utilization methods adhere to these basic criteria as will be evident in the discussion of the different methods. Nonetheless, each method has its potential strengths. Eight broad drug utilization methods are discussed, namely:\(^\text{(11)}\)

- methods used in qualitative studies;
- studies on prescription habits;
- studies on patient compliance;
- studies on drug effects;
- studies on patients’ knowledge about drugs;
- ad hoc studies;
- descriptive studies, determinants of drug utilization and impact of drug use; and
- consumption studies.

**Methods used in qualitative studies**

Identifying wide differences in the supply or use of drugs between countries or areas of a country does not necessarily indicate which of the various patterns identified is the preferred one. Also, the fact that a drug is widely used does not necessarily mean that good treatment is being provided. Various methods have been developed to determine the quality of drug usage and these methods can also be used for international comparisons. The four major parameters used in qualitative studies are the potential therapeutic value; expected degree of use; number of products with one active ingredient; and systems to limit the availability of drugs.\(^\text{(6,12)}\)

**Studies on prescription habits**

The second method used in drug utilization studies is to study prescription habits of medical practitioners. These studies aim to analyze the type of drugs prescribed, their dosing schedule, and the adequacy of the prescription for a specific diagnosis. By using data on prescriptions and prescribing, it is possible to relate prescribing patterns to many other aspects, for example, to:\(^\text{(11)}\)

- analyze patterns of drug use among patient categories defined by age, sex or diagnosis;
- study the relationship between the prescribed medicine and the apparent indication;
- identify the illnesses most frequently treated;
- identify and study prescription determinants, such as the extent to which prescribing has been influenced by particular information or publicity campaigns; and
A Review of Drug...

- examine specific safety problems in drug use in the light of actual practice.

Three major types of studies on prescription habits can be distinguished, namely studies on prescription prevalence, studies on therapeutic profiles, and medical record review.

**Studies on patient compliance**

The term compliance has been defined by Sackett and Haynes as "the extent to which the patient's behaviour (in terms of taking medications, following diets or executing other life-style changes) coincides with clinical prescription". Medication compliance specifically is thus the degree of agreement between prescription and behaviour in taking medicine. Various studies show that only a (variable) fraction of patients who are prescribed drug treatment actually do take it, though few studies have focused on the determinants of compliance. Studies on patient compliance aim to study whether prescribed drugs are administered to the patient in optimal conditions and to detect problems that may appear in this phase.

Traditionally, the sources of information for the measurement of drug compliance have fallen into two main groups, according to the techniques used to collect it. Direct techniques comprise methods such as measuring the level of a drug or its metabolites in blood or urine. Indirect techniques include evaluation of the number and type of drugs returned, studies on nursing compliance, and the voluntary incidence report system.

The assessment of drug compliance can also be approached from three other points of view. The first approach is based on methods used to study different aspects of patient behaviour in taking medicines, such as the number of doses taken during a certain period of time, the intervals between doses and the mode of administration. The second approach is based on methods used in the measurement of drug plasma levels, and the presence of drugs and their metabolites in other body fluids, considering the impact of variations in the absorption, distribution, metabolism and excretion of drugs. This method is the same as the direct method to measure medication compliance described above. The third approach is based on methods used to study clinical outcome. Clinical outcome may however be influenced by other factors besides patient medication behaviour. These three approaches may be regarded as representing three different levels in the chain from the prescription of medication to clinical outcome.

**Studies on drug effects**

The aim of these studies is to evaluate the effects of drugs in patients. The two main studies for this purpose are adverse drug reaction studies and studies on the perception of the effect of a drug. Adverse drug reaction studies are the most well-known type of study and can be performed by different epidemiological methods, for example correlation studies, cohort studies, case control studies and post-marketing surveillance studies. In quality assurance programs in hospital and at primary health care level, the most common studies about the effect of drugs are the ones that aim to compare patients' and providers' perceptions of the effect of the drug. These studies can be conducted for drugs whose effects can be clearly perceived by patients, for example analgesics and antibiotics. They are called tridimensional studies because they are usually made by means of a survey to patients and providers and a review of medical records.

**Studies on patients' knowledge about drugs**

Patients' knowledge about drugs is usually measured by surveys. The simplest type of survey inquires into the degree of knowledge of the patient about the drugs he or she is taking, their dosing schedule and indications. Other more sophisticated techniques compare by tape-recording of the doctor-patient interview, on the information provided by the doctor and a survey on the patients' understanding. Patients' knowledge can also be measured by indirect methods like patients' compliance of treatment, and it is also known that patients' compliance is related to the type of illness and the doctor-patient's relationship.

**Ad hoc studies**

Alongside all the techniques for drug utilization studies that are of general application, ad hoc studies are developed to meet a particular need or to exploit an unexpected opportunity. When generalized utilization
studies in Scandinavia and Northern Ireland revealed differences in the use of antihypertensive and antidiabetic drugs, ad hoc studies were performed to investigate possible explanations for the differences and to predict consequences\(^{(11,14,15)}\). A questionnaire survey was undertaken in a random sample of 400 general practitioners and hospital doctors\(^{(14,15)}\). They were asked to give their opinion on the choice of therapy for three model cases designed to cover the spectrum of treatment of type II diabetes and on the choice of antihypertensive drugs for analogous case histories relating to mild or moderate hypertension. Ad hoc studies may also be designed to focus on drug treatment patterns in particular population groups (for example, certain age groups, pregnant or lactating women).

**Descriptive studies, determinants of drug utilization and the impact of drug use**

Another classification used by some authors is to distinguish between three types of drug utilization studies, namely descriptive studies, determinants of drug utilization and the impact of drug use\(^{(16)}\). Descriptive studies serve to profile the present situation and to pinpoint problems. Different aspects may be stressed in descriptive studies, namely drug utilization of high risk groups in the population (for example, drug usage patterns in geriatric patients), drug utilization of specific drug groups (for example, benzodiazepines), trends in drug expenditure (for example, an overall change in volume due to changes in the morbidity pattern or a change in price), inter-doctor variation and drug utilization in small patient groups. Drug utilization is determined not only by the availability of the different products, but also by the knowledge and attitudes of healthcare professionals as well as the general public. Drug policy and drug information therefore influence drug utilization. Impact of drug use can be measured by studies on adverse effects and how the quality of life of patients is influenced by drug use.

**CONSUMPTION STUDIES**

Different ways of expressing drug consumption exist. Before an international unit of measurement of consumption was agreed upon, the consumption parameters most widely used in drug utilization studies included cost, numbers of units dispensed or sold and number of prescriptions. Although these parameters all have limitations when comparing drug consumption at the international level, they are nevertheless useful.

- **Cost studies**

Cost studies produced the first "drug statistics"\(^{(11)}\). These studies were initially carried out mainly by public health organizations to monitor expenditure on drugs. The quantification of drug consumption in economic terms can be useful in evaluating some aspects of the general health policy in a given country, particularly if drug expenditure is analyzed as a proportion of total health expenditure. Cost studies express drug use in terms of costs (for example, national currency). While cost figures are especially suitable for an overall cost analysis of drug expenditure, they are also applicable for prescription studies of only one substance. However, using data based on drug cost can introduce measurement errors because differential pricing occurs according to distribution channels employed, quantity purchased, import duties and currency exchange rate differences between countries, as well as the regulatory policies that affect pricing. These problems of interpretation of drug cost data are compounded by the different classification systems used for drugs in different countries. Studies based on cost data do not allow for cross-national comparisons, for comparisons between different programs within one country, or longitudinal studies. Consequently, cost data introduce considerable limitations in the interpretation of drug utilization studies.

- **Studies based on numbers of units sold**

In early drug utilization studies, gross drug sales data were the most commonly used indicator\(^{(1)}\). This information is widely available and can be obtained from manufacturers or wholesalers. Consideration of consumption in terms of "packages sold" gives a more precise idea of drug consumption than do economic value. This unit too has its limitations, especially when
studying changes over a period of time or comparing consumption between countries. Common physical units (for example, grams, kilograms and litres), and numbers of packages or tablets, are also used for quantifying drug consumption. These units can only be applied when the use of one drug (or well-defined products) is evaluated. Problems arise when the consumption of whole drug groups is considered. If consumption is given in terms of grams of active ingredients, drugs with a low potency will have a larger fraction of the total than drugs with a high potency. Combined products may also contain different amounts of active ingredients from plain products, which will not be reflected in the figures. Counting numbers of tablets also has disadvantages, because strengths of tablets vary, with the result that low strength preparations contribute more than high strength preparations. Short-acting preparations will therefore often contribute more than long-acting preparations (usually higher amounts of active ingredients).

**Studies on prescription volume**

The number of prescriptions issued (for example, from a health institution or in a given geographical area) has also been used as a measuring unit. Numbers of prescriptions do not give a good indication of total use, unless the total amount of drugs per prescription is being considered. Counting of prescriptions, however, is of great value in measuring the frequency of prescriptions and evaluating the clinical use of drugs (for example, diagnosis and dosages used). It may also reflect the prescriber/patient relationship and its variations over a period of time.

**The Defined Daily Dose (DDD)**

To overcome the limitations of expressing consumption in terms of costs or units prescribed or sold, another measurement unit was established and has come into widespread use, namely the Defined Daily Dose (DDD). A DDD is defined for each drug (that is, each active ingredient). A DDD corresponds to what is assumed to be the average dose per day for the drug, when used in its main indication in adults. The dosing levels have been defined according to recommendations in the medical literature, the manufacturer's advice in the data sheet, and experience gained in the field with the product concerned.

The DDD is purely a technical unit of measurement and comparison and, as such, provides a rough estimate of the proportion of patients within a community that would receive the drug treatment. It does not necessarily reflect the recommended or actual used dose. Many drugs are for instance used in different dosages for different indications and this must be taken into consideration when evaluating drug consumption figures. Sales or prescription data monitored and presented in DDDs will thus only give a rough estimate of consumption and not a real picture of actual use.

Two basic assumptions underlie the use of the DDD, namely that patients take the medication (that is, that patients are compliant); and the doses used for the major indication are the average maintenance doses.

By applying the DDD to a defined population, it is possible to:

- examine changes in drug consumption over time;
- make international comparisons;
- evaluate the effect of educational programs directed either at the prescriber or the patient;
- document the relative therapy intensity with various groups of drugs;
- follow changes in the use of a class of drugs; and
- evaluate regulatory effects on prescribing patterns.

Where possible, the DDD is indicated in terms of the weight of active substance using the most appropriate units, for example, g (gram), mg (milligram), ug (microgram), mmol (millimol), E (unit), TE (thousand units) or ME (million units). For practical reasons, the DDD is based on use in adults, except for certain preparations exclusively used in children. Where dosage is normally related to body weight, the daily dose is calculated on the assumption that the adult weighs 70 kg.
and the child 25 kg. For drugs administered in an initial loading dose that differs from the maintenance dose, the latter is chosen as a basis for the DDD. If a drug can be used for prophylaxis as well as for therapy, the therapeutic dose is generally chosen, except where the main indication is clearly prophylactic. The system has also been developed to allow for a number of problematic and fringe situations:

- For drugs used in different dosages according to the route of administration, for example, different daily doses may be established: one DDD may be used for the oral route and another for the parenteral route.
- For fixed combinations, where the defined dose cannot be expressed in weight of active substance, it is expressed as the number of single doses (such as the number of tablets, capsules or suppositories) normally used per day to obtain the desired therapeutic effect, following the same sources of information as those used to establish the DDD.

All DDDs for plain substances are based on monotherapy treatment. In some drug groups no DDDs are established since it is difficult to find appropriate DDDs, for example dermatologicals. All assigned DDDs are regularly reviewed because dosages may change over time due to, for instance, new main indications or newer research, and it may be necessary to make some alterations. Changes of DDDs are, however, kept to a minimum and are avoided as far as possible, because too many alterations are disadvantageous for long-term studies on drug utilization.

Consumption in a given geographical area is usually expressed in DDD per 1 000 inhabitants per day. This parameter provides a rough idea of the proportion of the population receiving a standard drug treatment every day. It does not indicate how many patients are actually being treated, however, except in the case of drugs used continuously (such as insulin or contraceptives). For example, a consumption level for an antibiotic or analgesic of 15 DDD per 1 000 inhabitants per day theoretically corresponds to 1.5% of the population on continuous treatment; but such drugs are more generally used over short periods, and the reality is probably closer to 15% of the population taking the drug for a month or 60% for a week\(^{(11)}\). In such cases, consumption is better expressed as DDD per inhabitant per year, making it easier to visualize what the figures mean in real terms.

Consumption in hospitals is calculated in the same way as consumption in the general population, but it is usually expressed as the number of DDD per 100 bed-days. In making the calculation, the days of admission and discharge are usually counted together as one bed-day.

Although the introduction of the DDD has meant a great improvement in the measurement of drug consumption, some problems and limitations exist that must be considered when interpreting these data, namely\(^{(11)}\):

- Consumption studies using the DDD methodology use data on units issued or sold. It is well known that not all drugs reaching the patient are necessarily consumed.
- It is important to consider, and adapt if necessary, the size of the population used as a denominator. Usually general consumption is calculated for the total population (all age groups), but drug use is often concentrated within certain specific groups (for example, oral contraceptives and some vaccines). In certain cases it can be more meaningful to take such a group as a denominator. The consumption, for example, of oral contraceptives is routinely given as the percentage of women 18 to 44 years old using these preparations.
- In the simplest situation, that is, where drugs are used continuously and for one indication only, the consumption given in terms of the DDD per inhabitant may roughly agree with the morbidity figures. This has been proven true for antidiabetic drugs, and particularly for the oral hypoglycaemic agents. By contrast, such a correlation for drugs used in several indications (for example, benzodiazepines or antipsychotics) or in short or variable courses of treatment (for example, analgesics or antibiotics) cannot be expected.
- The DDD methodology does not provide a means of profiling the extent to which fixed combinations are used. Although a specific unit has been defined for
combined preparations - the Effective Dose (ED)-it is not suitable for comparing the consumption of drugs between countries if different types and doses of fixed-dose combinations are used.

- The DDD is not necessarily equivalent to the average doses actually prescribed nor yet to the average dose actually ingested every day. The doses prescribed and taken in a particular community will vary with the indications actually predominating, national or regional therapeutic traditions, and with the attitude of patients.

- The Prescribed Daily Dose (PDD)

To overcome the inherent limitations of the DDD, the Prescribed Daily Dose (PDD) has been introduced to be used alongside the DDD\(^2,11\). The PDD represents the average prescribed dose in the main indication. The PDD more accurately reflects drug exposure than the DDD.

The PDD can be determined from prescription studies, medical records and patient interviews. It is of importance to relate the PDD to the diagnosis for which the dosage is based on. The PDD gives the average daily amount of the drug which is actually prescribed. When there is a substantial discrepancy between the PDD and the DDD, caution is needed when comparison is made. Studies have shown that although the difference between the DDD and the PDD is for some drugs quite small (for example, antihypertensives and antidiabetics)\(^17\), it may be appreciable in other fields of therapy (such as analgesics and psychotropic agents)\(^18\).

The PDD can vary according to both the illness treated and national therapy traditions. For antiinfectives, for instance, PDDs vary according to the severity of the infection. The DDDs for most antiinfectives are based on treatment of moderately severe infections. In hospital care, much higher doses are frequently used and this must be considered when using the DDD as a unit of measurement.

Applications of the DDD and PDD

Drug utilization studies are normally done in hospital or ambulatory care settings. Limited research has been conducted on drug utilization in community pharmacy due to the difficulty in generating the necessary data in this setting. Inesta\(^19\) has developed another unit, namely the Defined Daily Dose/100 consumers/day (DCD), for the determination of drug utilization from community pharmacy records allocated in cities where it is difficult to estimate the population covered by each pharmacy. Stanulovic and others\(^20\) investigated the possibility of adapting the DDD methodology to paediatric use. He used the rule of the fraction of the body surface area as the fraction of adult dose, represented as a DDD. In most of the calculations, one sixth of the DDD was taken for infants up to three months of age, one fifth for infants aged 3 to 12 months, one third for children aged 1 to 3 years, and one half for children of 3 to 14 years of age.

More recently, methods to estimate basic epidemiologic measures of drug utilization and methods to screen for aberrant prescribing patterns have become widely used, especially for individual-level pharmacy dispensing data\(^21\). Examples include therapeutic intensity, prevalence, incidence, duration index, the Lorenz curve and waiting-time distributions\(^21\). Further useful methods include the DU90%\(^22\) and DC90%.

Drug classification systems

The need for a single international classification system as a tool for performing comparative drug utilization studies was felt from an early phase of drug utilization research. Medicines can be classified in various ways: according to their mode of action, the pharmacological or therapeutic groups to which they belong, according to their indications, or according to their structure. Various systems were proposed and used experimentally over the years. In the Anatomical Therapeutic Chemical (ATC) classification system, drugs are divided into different groups according to their site of action and therapeutic and chemical characteristics\(^23\). The ATC/DDD system was initially developed as a tool for presenting drug consumption figures. The system has shown itself to be suitable for comparisons of drug consumption both nationally and internationally. The ATC/DDD system can also provide a basis for the evaluation of long-term trends in drug use. The ATC
system has been recommended by the WHO for drug utilization studies so that data throughout the world can be comparable\(^2\). According to the ATC classification system, drugs are divided into 14 main groups. Each drug group has two divisions (a second and third level), which are therapeutic subgroups. The ATC system also contains a fourth and fifth level for the chemical/therapeutic subgroup and for the single chemical substance.

The ATC system, if employed universally, could facilitate international comparisons for drug consumption studies. Each pharmaceutical preparation has only one ATC code, although a drug may be used in two or more equally important indications. A drug may also be available in two or more strengths with clearly different therapeutic uses. The use of the drug usually determines the classification. Combination products are categorised by principal use. For example, a drug containing an analgesic and a tranquilliser that has, as its principal use, the alleviation of pain, is classified as an analgesic.

**CONCLUSION**

A basic outline was given in this article of drug utilization. It is difficult to attempt to evaluate the effectiveness of all the drug utilization methods discussed. There is not yet enough evidence to recommend one method over another and choices should therefore be made according to the specific objectives of each study and the level at which it is performed. If drug utilization studies are to be reliable, they will have to adhere to strict methodological standards, the most basic of which continue to be the use of a common drug classification system and of an international unit of measurement.
A Review of Drug...

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