

Introduction to Drug Utilization Research 2003

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**World Health Organization**

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## PREFACE:

### DRUG UTILIZATION RESEARCH - THE EARLY WORK

The development of drug utilization research was sparked by initiatives taken in Northern Europe and the United Kingdom in the mid-1960s (1, 2). The pioneering work of Arthur Engel in Sweden and Pieter Siderius in Holland (3) alerted many investigators to the importance of comparing drug use between different countries and regions. Their demonstration of the remarkable differences in the sales of antibiotics in six European countries between 1966 and 1967 inspired WHO to organize its first meeting on «Drug consumption» in Oslo in 1969 (4). This led to the constitution of the WHO European Drug Utilization Research Group (DURG).

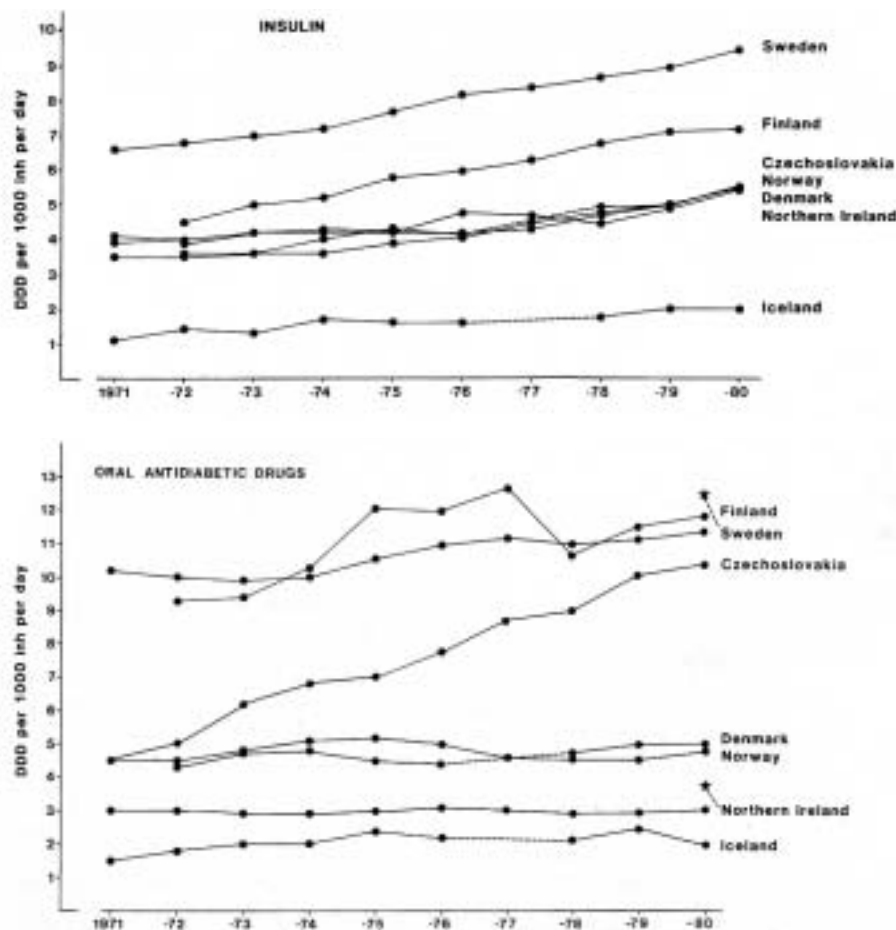
The pioneers of this research understood that a correct interpretation of data on drug utilization requires investigations at the patient level. It

became clear that we need to know the answers to the following questions:

- why drugs are prescribed;
- who the prescribers are;
- for whom the prescribers prescribe;
- whether patients take their medicines correctly;
- what the benefits and risks of the drugs are.

The ultimate goal of drug utilization research must be to assess whether drug therapy is rational or not. To reach this goal, methods for auditing drug therapy towards rationality are necessary.

The early work did not permit detailed comparisons of the drug utilization data obtained from different countries because the source and form of the information varied between them. To overcome this difficulty, researchers in Northern Ireland (United Kingdom), Norway and Sweden



**Figure 1** Utilization of insulin and oral antidiabetic drugs in seven European countries from 1971-1980 expressed in defined daily doses (DDDs) per 1000 inhabitants per day. For comparison the prescribed daily doses (PDD) per 1000 inhabitants per day of oral antidiabetic drugs are given for Northern Ireland (UK) and Sweden for 1980 (indicated with an asterisk).

developed a new unit of measurement, initially called the agreed daily dose (5) and later the defined daily dose (DDD) (6). This unit was defined as **the average maintenance dose of the drug when used on its major indication in adults**. The first study used antidiabetic drugs as an example: it was found that the sum of the DDDs of insulin and oral antidiabetic drugs (about 20 DDDs per 1000 inhabitants per day) roughly corresponded to the morbidity due to diabetes after correction for the number of patients treated with dietary regimens alone. Among the first countries to adopt the DDD methodology was the former Czechoslovakia (7) and the first comprehensive national list of DDDs was published in Norway in 1975 (8). Another important methodological advance was the adoption of the uniform anatomical therapeutic chemical (ATC) classification of drugs (see chapter 5.2). The use of standardized methodology allowed meaningful comparisons of drug use in different countries to be made (Fig. 1).

Drug utilization research developed quickly during the following 30 years and soon became a respectable subject for consideration at international congresses in pharmacology, pharmacy and epidemiology. Particularly rapid developments were seen in Australia (9) and Latin America (10). The number of English-language papers on the subject listed in the *Cumulative index medicus* rose from 20 in 1973 (when the term «drug utilization» first appeared) to 87 in 1980, 167 in 1990, and 486 in 2000.

History has taught us that successful research in drug utilization requires multidisciplinary collaboration between clinicians, clinical pharmacologists, pharmacists and epidemiologists. Without the support of the prescribers, this research effort will fail to reach its goal of facilitating the rational use of drugs.

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# CHAPTER 1: WHAT IS DRUG UTILIZATION RESEARCH AND WHY IS IT NEEDED?

## 1.1. DEFINITION AND DOMAINS

[ *Drug utilization; pharmacoepidemiology; pharmacosurveillance; pharmacovigilance* ]

• **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** has been 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 modern 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, for example, by means of 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 (educational) 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 data on drug utilization to figures on morbidity, outcome of treatment and quality of care with the ultimate goal of assessing 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, and comparisons of 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. Over time, 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 that focus on drugs (e.g. aggregate data from wholesale and prescription registers) the term epidemiology implies defined populations in which drug use can be expressed in terms of incidence and prevalence (see chapter 1.2.1).

Together, drug utilization research and pharmacoepidemiology may provide insights into the following aspects of drug use and drug prescribing.

• **Pattern of use:** This covers the extent and profiles of drug use and the trends in drug use and costs over time.

• **Quality of use:** This is determined using audits to compare actual use to national prescription guidelines or local drug formularies.<sup>1</sup> Indices of quality of drug use may include the choice of drug (compliance with recommended assortment), drug cost (compliance with budgetary recommendations), drug dosage (awareness of inter-individual variations in dose requirements and age-dependence), awareness of drug interactions and adverse drug reactions, and the proportion of patients who are aware of or unaware of the costs and benefits of the treatment.

• **Determinants of use:** These include user characteristics (e.g. sociodemographic parameters and attitudes towards drugs), prescriber characteristics (e.g. speciality, education and factors influencing therapeutic decisions) and drug characteristics (e.g. therapeutic properties and affordability).

<sup>1</sup> 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.

- **Outcomes of use:** These are the health outcomes (i.e. the benefits and adverse effects) and the economic consequences.

The initial focus of pharmacoepidemiology was on the safety of individual drug products (pharmacovigilance), but it now also includes studies of their beneficial effects. The driving force behind this development was a growing awareness that the health outcomes of drug use in the rigorous setting of randomized clinical trials are not necessarily the same as the health outcomes of drug use in everyday practice. The clinical trials needed to obtain marketing authorization for new drugs involve limited numbers of carefully selected patients, who are treated and followed-up for a relatively short time in strictly controlled conditions. As a result, such trials do not accurately reflect how drug use will affect health outcomes in everyday practice under everyday circumstances. Pharmacoepidemiological studies often make useful contributions to our knowledge about effectiveness and safety, because, unlike clinical trials, they assess drug effects in large, heterogeneous populations of patients 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 and the results of such research can be used to help to set priorities for the rational allocation of health care budgets.

## 1.2 WHY DRUG UTILIZATION RESEARCH?

*Description of drug use pattern; early signals of irrational use of drugs; interventions to improve drug use; quality control cycle; continuous quality improvement*

The principal aim of drug utilization research is to facilitate the rational use of drugs in populations. For the individual patient, the rational use of a drug implies the prescription of a well-documented drug at an optimal dose, together with the correct information, at an affordable

price. Without a knowledge of how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use or to suggest measures to improve prescribing habits.

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 important ways as described below.

### 1.2.1 DESCRIPTION OF DRUG USE PATTERNS

Drug utilization research can increase our understanding of how drugs are being used as follows.

- It can be used to estimate the numbers of patients exposed to specified 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**).
- It can describe the extent of use at a certain moment and/or in a certain area (e.g. in a country, region, community or hospital). Such descriptions are most meaningful when they form part of a continuous evaluation system, i.e. when the patterns are followed over time and trends in drug use can be discerned.
- Researchers can estimate (e.g. on the basis of epidemiological data on a disease) to what extent drugs are properly used, overused or underused.
- It can determine the pattern or profile of drug use and the extent to which alternative drugs are being used to treat particular conditions.
- It can be used to compare the observed patterns of drug use for the treatment of a certain disease with current recommendations or guidelines.
- It can be used in the application of quality indicators to patterns of drug utilization. An example is the so-called DU90% (drug utilization 90%), a further development of the «top-ten» list.

The DU90% segment reflects the number of drugs that account for 90% of drug prescriptions

and the adherence to local or national prescription guidelines in this segment. This general indicator can be applied at different levels (e.g. individual prescriber, group of prescribers, hospitals, region or county) to obtain a rough estimate of the quality of prescribing.

- Drug utilization data can be fed back to prescribers. This is particularly useful when the drug prescribing by a particular individual can be compared with some form of «gold standard» or best practice, and with the average prescriptions in the relevant country, region or area.
- The number of case reports about a drug problem or adverse effects can be related to the number of patients exposed to the drug 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 given dose level, improving the information on indications, contraindications and appropriate dosages may be sufficient to ensure safer use and avoid withdrawal of the drug from the market.

### 1.2.2 EARLY SIGNALS OF IRRATIONAL USE OF DRUGS

Drug utilization research may generate hypotheses that set the agenda for further investigations as outlined below, and thus avoid prolonged irrational use of drugs.

- Drug utilization patterns and costs between different regions or at different times may be compared. 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 in drug use over time may have medical, social and economic implications both for the individual patient and for society, and should therefore be identified, explained and, when necessary corrected.
- The observed patterns of drug use can be compared with the current recommendations and guidelines for the treatment of a certain disease. Hypotheses can then be generated to determine whether discrepancies represent less than opti-

mal practice, whether pedagogic interventions (education) are required or whether the guidelines should be reviewed in the light of actual practice. These hypotheses should apply to both under use and over use of drugs.

### 1.2.3 INTERVENTIONS TO IMPROVE DRUG USE - FOLLOW-UP

Drug utilization research undertaken in the following ways may enable us to assess whether interventions intended to improve drug use have had the desired impact.

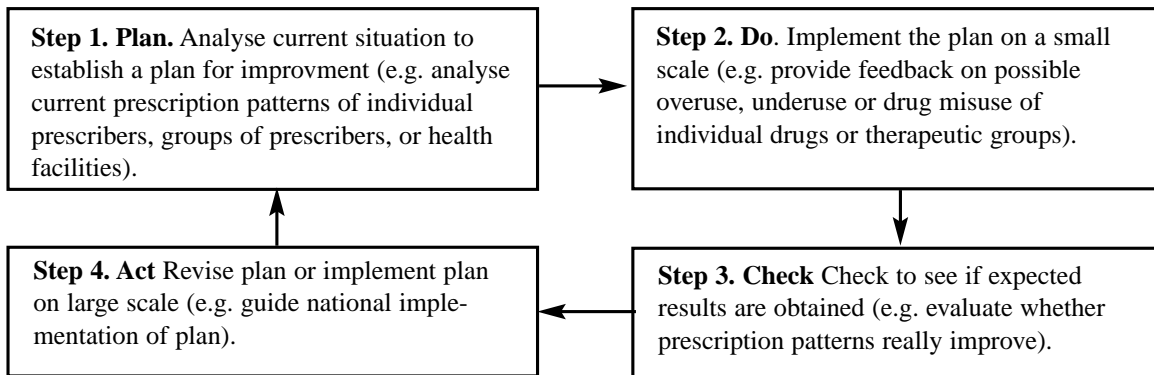
- The effects of measures taken to ameliorate undesirable patterns of drug use (e.g. provision of regional or local formularies, information campaigns and regulatory policies) should be monitored and evaluated. The researchers should bear in mind that prescribers may have switched to other drugs that are equally undesirable. These potential alternative drugs should be included in the survey to assess the full impact of the measure.
- The impact of regulatory changes or changes in insurance or reimbursement systems should be assessed using a broad survey. This is necessary because the total cost to society may remain the same or may even increase if more expensive drugs are used as alternatives.
- The extent to which the promotional activities of the pharmaceutical industry and the educational activities of the society affect the patterns of drug use should be assessed.

### 1.2.4 QUALITY CONTROL OF DRUG USE

Drug use should be controlled according to a **quality control cycle** that offers a systematic framework for **continuous quality improvement**. The components of such a cycle are illustrated on the next page.

After step 4, the cycle begins again with new analyses, the setting of new targets, and so on.

The quality control cycle can be applied at many levels, ranging from local or regional discussion groups consisting of physicians, clinical pharmacologists or pharmacists to national and



international initiatives. An important technique that can be used in conjunction with this cycle is **benchmarking**. By comparing drug utilization data from different localities, it is often possible to detect substantial differences that require further evaluation, which may then lead to the identification and promotion of best practice. Such comparisons will be accurate and truthful provided that the data are collected and aggregated in a standardized, uniform way (see chapter 5).

### 1.3 DRUG UTILIZATION STUDIES AND DRUG POLICY DECISIONS

Many of the questions asked in drug utilization research and the answers obtained are important for initiating and modifying a rational drug policy at both national and local levels. Two successful examples of the use of such research are given below.

#### *Drug use in Estonia*

An important reason for undertaking studies of drug use in Estonia after its independence was the need to make decisions on drug policy. At the time, no information was available in the country on which drugs were used (sold), or on the quantities and there was therefore no rationale for regulating the drug market. Moreover, in the absence of any feedback system it was impossible to gauge the impact of possible future interventions. A national drug classification system was therefore developed for Estonia, and a reporting system from wholesalers, based on this classification, was implemented, checked

and validated from 1992-1994. Since then, annual reviews of drug utilization have been used to provide background information for decisions on regulatory and reimbursement policies in Estonia; two examples are described below.

If physicians have high rates of inappropriate prescribing, drug regulatory authorities can require educational intervention or impose restrictions on specific drugs or on practitioners. In Estonia, it was decided to stop the import and use of some hazardous products, such as phenacetine, older sulphonamides and pyrazolones, after clarifying and explaining the reasons for this in the national *Drug information bulletin*, which is distributed free by the drug regulatory authority to all prescribers in Estonia.

In planning the reimbursement policies, the total volume of drug use in DDDs was monitored carefully. During the 1990s, the use of prescription-only medicines measured as number of DDDs per capita was less than one third of that reported from the Nordic countries. This proved to be the result of under-treatment of certain chronic diseases (i.e. hypertension and schizophrenia), and therefore the decision was to increase the availability and use of cardiovascular and neuroleptic drugs. Thus, the national drug use surveys in Estonia have been used to monitor the impact of drug regulatory activities as well as to follow the increase in drug expenditure. Because data on drug use are only part of the background material relevant to the discussions and decisions on therapeutic strategies - at both the local and national levels - it is difficult to

evaluate the specific influence of drug utilization research on developments in drug policies. It is, however, reasonable to assume that such studies have contributed to a more rational use of drugs in Estonia.<sup>1</sup>

#### *Drug use in Latin America*

The second example is the successful work within the Latin American DURG, in association with the WHO Collaborating Centre of Pharmacoepidemiology in Barcelona, Spain.

In September 1991, health professionals from Spain and eight Latin American countries met in Barcelona for the «First Meeting of Latin American Groups for Drug Epidemiology». It was made clear that in most of the countries taking part, data on drug utilization were scarce and fragmentary. Some national drug regulatory authorities had no access to either quantitative or qualitative data on drug consumption and realized that information on patterns of drug utilization would be useful for designing drug policy and educational programmes about drugs.

It was agreed at this meeting to set up a Latin American network (later called DURG-LA), with the following aims:

- to promote drug utilization research in Latin American countries;
- to exchange experiences and information between the participating groups;
- to use the knowledge generated to give technical advice to drug regulatory authorities and to guide teaching of pharmacology;
- to write and disseminate information aimed at improving drug use, and
- to participate in the training of health professionals in pharmacoepidemiology and therapeutics.

Seven further DURG-LA meetings have been held over the subsequent ten years to promote drug utilization research. Part of the initial core group participated in a first multicentre study in six Latin American countries to examine self-medication and self-prescription. The study was carried out in a sample of pharmacies from diffe-

rent social-class districts in the catchment areas of 11 health centres.<sup>1</sup>

#### 1.4 GENERAL READING

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<sup>1</sup> The information about DURG-LA was provided in a personal communication by Dr Albert Figueras and Professor Joan-Ramon Laporte, Barcelona, Spain.

Different types of drug use information are required depending on the problem being examined. These include information about the overall use of drugs, drug groups, individual generic compounds or specific products. Often, information about the condition being treated, the patient and the prescriber is also 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 in detail below, together with examples to illustrate the ways in which the information can be used to promote the rational use of drugs.

### 2.1 DRUG-BASED INFORMATION

Knowledge of the trends in total drug use may be useful, but more detailed information involving aggregation of data on drug use at various levels, and information on indications, doses and dosage regimens is usually necessary to answer clinically important questions.

#### 2.1.1 LEVEL OF DRUG USE AGGREGATION

The level at which data on drug use are aggregated will depend on the question being asked. For example, the question might concern the relative use of drug groups in the treatment of hypertension. It would then be appropriate to aggregate data on diuretics, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, etc. If, however, the question concerns the relative use of beta-blockers in hypertension, data at the substance (generic drug) level would be needed. Information on the relative scale of use of individual products will sometimes be required, for example to find the market leader or to assess the relative use of generic versus branded or innovator products. Information down to the level of dose strength will be necessary, for example, to determine whether there is a trend towards use of higher strengths of antibiotics, or to determine the relative use of strengths of antidepressants to assess whether they are being used at effective doses.

#### 2.1.2 INDICATION

For drugs with multiple indications, it will usually be important to divide data on use according to indication to allow a correct interpretation of the overall trends. An example is the relative use of drug groups in treating hypertension. The overall data might suggest that the relative use of diuretics is comparable to that of ACE inhibitors and higher than the use of calcium channel blockers (column A in Table 1). However, analysis of the data according to indication may reveal that 75% of ACE inhibitors are used to treat hypertension whereas only 43% of diuretics are used for this indication (most of the high-ceiling diuretics used are for treating heart failure). The picture that emerges of the use of the two drug groups in the treatment of heart failure is markedly altered when use according to indication is taken into account (column B of Table 1).

*Table 1 Relative use of drug groups in the treatment of hypertension in Australia in 1998<sup>a</sup>*

Drug group	A <sup>b</sup>	B <sup>c</sup>	C <sup>d</sup>
ACE inhibitors (C09A)	31.80	36.6	34.8
Calcium channel blockers (C08C)	24.50	28	26.7
Diuretics (C03)	29.60	19.4	15.9
Beta-blockers (C07AA, C07AB)	11.20	11.5	15.7
ATII antagonists (C09CA)	3.00	4.6	6.9

Source: Australian Drug Utilization Subcommittee and BEACH Survey April-December 1998, Sydney University, GPSCU 1999.

<sup>a</sup> Values are the use of the drug group expressed as a percentage of the total use for these drug groups.

<sup>b</sup> Based on total use.

<sup>c</sup> Adjusted for the percentage of total use of each group for the treatment of hypertension.

<sup>d</sup> Relative prescribing of these drug groups in hypertension community practice patient encounters.

Another example of a situation in which the indication is important is antibiotic utilization. In determining whether the use of a particular antibiotic, for example, amoxicillin, is rational, it will usually be necessary to know what infections or problems it is being used to treat. It would therefore be necessary to break down data on amoxicillin use into indications and compare these uses with the appropriate guidelines. If it were found that there was substantial use of amoxicillin to treat acute sore throat, for example, this finding would indicate a problem that needed to be addressed. This is because a narrow-spectrum agent (or no drug) would be a more appropriate treatment for a sore throat, and if amoxicillin is used to treat mononucleosis, which can present as a sore throat, there is a high incidence of rash.

### 2.1.3 PRESCRIBED DAILY DOSES

The prescribed daily dose (PDD) is the average daily dose prescribed, as obtained from a representative sample of prescriptions. The use of DDD per 1000 inhabitants per day allows aggregation of data across drug groups and comparisons between countries, regions and health facilities. However, the DDD metric may not reflect the actual PDDs, and this needs to be considered

when making such comparisons. The PDDs differ between countries and ethnic groups, and even between areas or health facilities within the same country. The PDD will also often differ for different indications of the same drug, so it will sometimes be necessary to reach this level of detail to interpret overall use data.

Data on the use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) in Australia are shown in Table 2 as both DDDs and prescription volumes.

The two metrics give different results for the relative use of the two groups of antidepressant drugs because of the different relationship between the PDDs and the DDDs for the two drug groups. On average, the PDD is lower than the DDD for the tricyclics and higher for the SSRIs. In this case, knowledge of the PDDs is necessary for clinical interpretation of the data.

The DDD per 1000 inhabitants per day is often used to derive a rough estimate of the prevalence of use in the population being studied, and for chronic diseases it may even be used to assess the prevalence of a disease when the drug is prescribed for a single indication. Such estimates are valid only if the DDDs and the PDDs are similar.

**Table 2** Relative use of antidepressants in Australia in 1998

	Prescription volume (millions) <sup>a</sup>	% of total prescription volume	DDD/1000 population/day	% of total DDD/1000 population/day
Tricyclics (N06AA)	3.53	48.82	8.40	28.09
SSRI (N06AB)	3.09	42.74	17.20	57.53
Moclobemide (N06AG02)	0.61	8.44	4.30	14.38
<b>Total</b>	<b>7.23</b>	<b>100.00</b>	<b>29.90</b>	<b>100.00</b>

Source: Australian Drug Utilization Subcommittee, Department of Health & Aged Care, Commonwealth of Australia, <http://www.health.gov.au:80/haf/docs/asm.htm>

## 2.2 PROBLEM OR ENCOUNTER-BASED INFORMATION

*Reason for the encounter (the problem); drug treatment versus non-drug treatment; other problems managed; severity of the problem managed; new or continuing presentation; duration of consultation; medications prescribed for the problem; how the medications were supplied; other medications prescribed*

Rather than asking how a particular group of drugs is used, it may be useful to address the question of how a particular problem (e.g. sore throat, hypertension or gastric ulcer) is managed. The different types of information that may be required are listed in the box above.

As an example, consider how problem-based information about the management of hypertension might be used. Initially, concordance with guidelines for drug treatment or non-drug management of blood pressure and other risk factors might be assessed. Where drug treatment is used, the proportion of patients treated with each of the drug groups gives an overall picture of management (column C of Table 1). This is more direct information on how hypertension is managed than that provided by assessing the overall use of the different drug groups as discussed above. In the example shown in Table 1, the data in columns B and C are reasonably con-

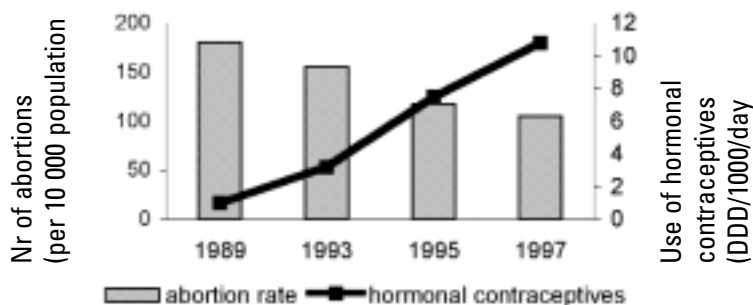
sistent. This consistency between data using two different approaches (i.e. drug and problem-based) gives confidence in the result.

Other questions that might be addressed using a problem-based approach include the following:

- Does the severity of hypertension influence the choice of single or combination therapy?
- Is the management of newly-presenting patients different to that of patients already receiving treatment?
- Are there likely to be any drug interactions with co-prescribed treatments?
- Is the choice of drug influenced by evidence-based outcome data?

For some diseases it may be important to study the relative use of drug treatment and other therapeutic approaches to map out and understand pharmacotherapeutic traditions and other therapeutic approaches. As an example, drug utilization research in Estonia has shown that there was a reciprocal relationship between the use of hormonal contraceptives and the abortion rate from 1989-1997 (Fig. 2).

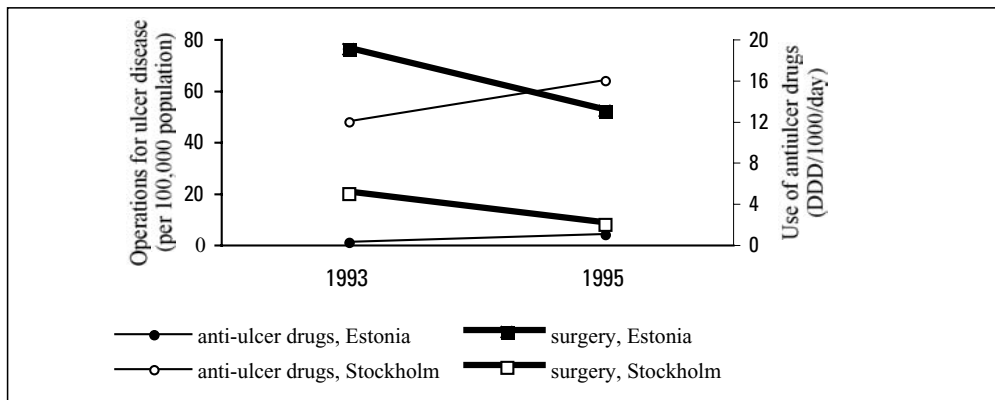
Another example was the excessive use of ulcer surgery in Estonia compared to Sweden during the Soviet era. This was because of the difficulties of obtaining modern anti-ulcer drugs in Estonia at that time (Fig. 3).



**Figure 2** Abortion rate and use of hormonal contraceptives in Estonia in 1989-1997.

Source: Kiivet R. Drug utilization studies as support to decisions in drug policy in Estonia. [MD Thesis] Stockholm, Karolinska Institutet, 1999.





**Figure 3** Treatment of ulcer disease in Estonia and in Stockholm County 1993-1995.  
 Source: Kiivet R. Drug utilization studies as support to decisions in drug policy in Estonia. [MD Thesis] Stockholm, Karolinska Institutet, 1999.

### 2.3 PATIENT INFORMATION

[ Age; gender; ethnicity; co-morbidities; knowledge; beliefs and perceptions ]

Information on demographic factors and other details about the patient will often be useful. For example, the age distribution of patients may be of critical importance, to assess the likelihood of severe adverse effects with nonsteroidal anti-inflammatory drugs (NSAIDs), or whether the drug is being used to treat patients in an age group different from that in which the clinical trials were performed. The co-morbidities of the patient group may be important in determining the choice of treatment and predicting possible adverse effects. For instance, in the management of hypertension, beta-blockers should not be used to treat patients with asthma, and ACE inhibitors are the preferred treatment in patients with heart failure.

Qualitative information relating to the knowledge, beliefs and perceptions of patients and their attitudes to drugs will be important in some cases, for example in assessing the pressures put by patients on their doctors to prescribe antibiotics, or in designing consumer information and education programmes.

### 2.4 PRESCRIBER INFORMATION

[ Demographic information - age, gender, medical school, years in practice; type of practice (e.g. specialist or family, rural or urban); practice size; patient mix; knowledge about drugs; factors driving prescribing behaviour ]

The prescriber plays a critical role in determining drug use. Claims have even been made that the differences between doctors are greater than those between patients and that variations in drug prescribing behaviour often lack rational explanations. Dissecting the factors that determine prescribing behaviour is therefore often central to understanding how and why drugs are prescribed. Some questions that might be addressed using prescriber information include the following:

- Are prescribing profiles influenced by the prescriber's medical education?
- Do the prescribing profiles of specialists differ from those of family practitioners?
- Does the age or gender of the prescriber influence the prescribing profile?
- Are there differences in prescribing behaviour between urban and rural practices or between small and large practices? Do these variations indicate a need to target education to particular sectors?

- Who are those prescribers who rapidly adopt recently released drugs?
- In assessing rational use of medicines by a practitioner, has the practice mix been taken into account?
- Can the factors that determine and change prescribing behaviour be identified?

## 2.5 TYPES OF DRUG UTILIZATION STUDY

Drug utilization studies can be targeted towards any of the following links in the drug-use chain:

- the *systems and structures* surrounding drug use (e.g. how drugs are ordered, delivered and administered in a hospital or health care facility);
- the *processes* of drug use (e.g. what drugs are used and how they are used and does their use comply with the relevant criteria, guidelines or restrictions); and
- the *outcomes* of drug use (e.g. efficacy, adverse drug reactions and the use of resources such as drugs, laboratory tests, hospital beds or procedures).

### *Cross-sectional studies*

Cross-sectional data provide a «snapshot» of drug use at a particular time (e.g. over a year, a month or a day). Such studies might be used for making comparisons with similar data collected over the same period in a different country, health facility or ward, and could be drug-, problem-, indication, prescriber- or patient-based. Alternatively, a cross-sectional study can be carried out before and after an educational or other intervention. Studies can simply measure drug use, or can be criterion-based to assess drug use in relation to guidelines or restrictions.

### *Longitudinal studies*

Public health authorities are often interested in trends in drug use, and longitudinal data are required for this purpose. Drug-based longitudinal data can be on total drug use as obtained through a claims database, or the data may be based on a statistically valid sample of pharmacies or medical practices. Longitudinal data are

often obtained from repeated cross-sectional surveys (e.g. IMS (Intercontinental Medical Statistics) practice-based data are of this type). Data collection is continuous, but the practitioners surveyed, and therefore the patients, are continually changing. Such data give information about overall trends, but not about prescribing trends for individual practitioners or practices.

### *Continuous longitudinal studies*

In some cases continuous longitudinal data at the individual practitioner and patient level can be obtained. Claims databases are often able to follow individual patients using a unique (but anonymous) identifier. These data can provide information about concordance with treatment based on the period between prescriptions, co-prescribing, duration of treatment, PDDs and so on. As electronic prescribing becomes more common, databases are being developed to provide continuous longitudinal data comprising full medical and prescribing information at the individual patient level. Such databases are very powerful, and can address a range of issues including reasons for changes in therapy, adverse effects and health outcomes.

## 2.6 DRUG COSTS

*Total drug costs; cost per prescription; cost per treatment day, month or year; cost per defined daily dose (DDD); cost per prescribed daily dose (PDD); cost as a proportion of gross national product; cost as a proportion of total health costs; cost as a proportion of average income; net cost per health outcome (cost-effectiveness ratio); net cost per quality adjusted life-year (cost-utility-ratio)*

Data on drug costs will always be important in managing policy related to drug supply, pricing and use. Numerous cost metrics can be used and some of these are shown in the box above. For example, the cost per DDD can usually be used to compare the costs of two formulations of the

same drug. However, it is usually inappropriate to use this metric to compare the costs of different drugs or drug groups as the relationship between DDD and PDD may vary.

Estimates of the costs at various levels and using data aggregated in various ways will be required, depending on the circumstances and the perspective taken. A government perspective might require information on drug costs and cost offsets to government to be collected, whereas a societal perspective would require both government and non-government (private sector) costs and cost offsets to be determined. A patient perspective will be appropriate if questions about affordability and accessibility are being asked. Costs may be determined at government, health facility, hospital, health maintenance organization or other levels within the health sector.

Costs will often need to be broken down according to drug group or therapeutic area to determine, for example, the reason for an increase in drug costs. For instance, the introduction of new, expensive anti-cancer agents may be found to be driving the increases in drug costs in a hospital. Changes in drug costs can result from changes in prescription volumes, quantity per prescription or in the average cost per prescription. For example, most countries have experien-

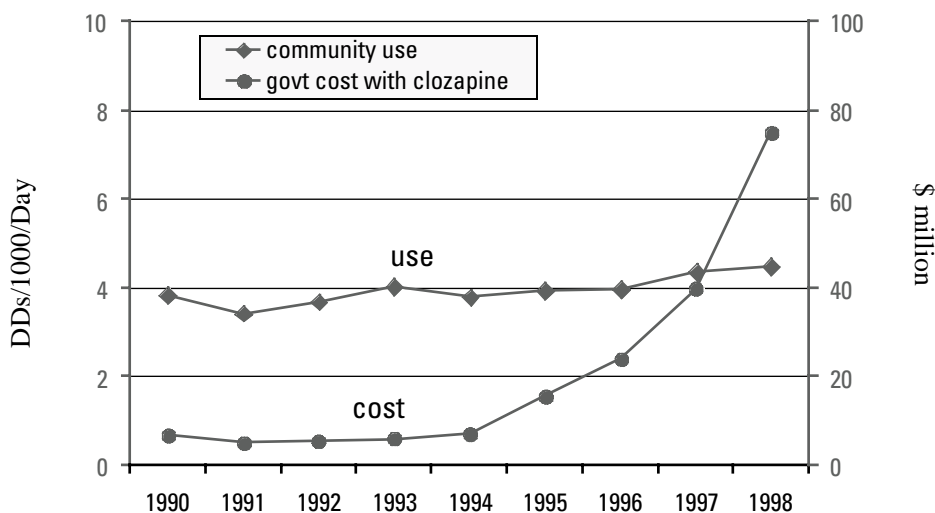
ced a marked increase in the cost of anti-psychotic drugs over the last 5-10 years; the data on use and cost for these drugs in Australia are illustrated in Fig. 4.

In Australia, there has been little increase in the overall volume of use of antipsychotic drugs, and the cost increase has been driven by the transfer from the cheap 'classical' agents to the much more expensive 'atypical' drugs such as clozapine, olanzapine and risperidone resulting in an increase in the average cost per prescription. In contrast, both the prescription volume of antidepressant drugs and the average cost per prescription have increased over the same period, due to an 'add-on' prescribing effect of the more expensive SSRIs.

## 2.7 GENERAL READING

Einarsson TR, Bergman U, Wiholm BE. Principles and practice of pharmacoepidemiology. In: Speight TM, Holford NH, eds. *Avery's Drug Treatment*. Place, Adis International, 1999:371-392.

Lee D, Bergman U. Studies of drug utilization. In: Strom B. ed. *Pharmacoepidemiology*, 3rd ed. Chichester, J Wiley, 2000:463-481.



**Figure 4** Antipsychotic drugs - use and cost trends in Australia

## 2.8 EXERCISES

### 3. Amoxicillin

You note that amoxicillin use expressed as DDDs per 1000 population per day has increased over the last two years. What types of drug utilization data would you need to evaluate the possible reasons for this?

### 4. Antidepressant use

The use of antidepressant drugs (in DDDs per 1000 population per day) and their costs have been increasing for at least the last five years. What types of data would you need to determine the reasons for the change and whether it has resulted in positive or negative health outcomes?

[ *Drug-use chain; large databases; other sources; drug use evaluation; pharmacoconomics* ]

The drug-use chain includes the processes of drug acquisition, storage, distribution, prescribing, patient compliance and the review of outcome of treatment. Each of these events is an important aspect of drug utilization, and most countries have regulations to cover these aspects. Data are collected, or are available, at national, regional and local health facility or household level and may be derived from quantitative or qualitative studies. Quantitative data may be used to describe the present situation and the trends in drug prescribing and drug use at various levels of the health care system.

Quantitative data may be routinely collected data or obtained 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 is intended to improve 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 care known as pharmacoconomics (see chapter 4).

The sources of drug utilization data vary from country to country depending on the level of sophistication of record keeping, data collection, analysis and reporting and the operational considerations of the health care system.

### 3.1 LARGE DATABASES

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 collected on drug sales, drug movement at various levels of the

drug distribution chain, pharmaceutical and medical billing or samples of prescriptions. The databases may be international, national or local in scope. They may be diagnosis-linked or non-diagnosis-linked. Diagnosis-linked data enable drug use to be analysed according to patient characteristics, therapeutic groups, diseases or conditions and, in the best of cases, clinical outcome. A useful analysis requires an understanding of the sources and organization of the data.

### 3.2 DATA FROM DRUG REGULATORY AGENCIES

[ *Drug registration; drug importation* ]

Drug regulatory agencies have the legal responsibility of ensuring the availability of safe, efficacious and good-quality drugs in their country. They are thus the repositories of data on which drugs have been registered for use, withdrawn or banned within a country. Regulatory agencies also have inspection and enforcement functions, and are responsible for supervising the importation of drugs and for the issuance of permits for drug registration.

It is possible, therefore, to obtain data on the number of drugs registered in a country from such agencies. Where the agency issues import permits and supervises drug importation, data on product type (i.e. generic or branded), volume, port of origin, country of manufacture, batch number and expiry date may be collected. Where the data reflect total national imports, estimates of quantities of drugs in circulation can be obtained for defined periods and for various therapeutic groups.

It may be difficult to obtain true estimates if documentation is incomplete and not all transactions are recorded. Information on smuggled goods or goods entering the country through illegal routes will not be captured by these data.

### 3.3 SUPPLIER (DISTRIBUTION) DATA

[ *Drug importation; local manufacture; customs service* ]

Data on suppliers may be obtained from drug importers, wholesalers or local manufacturers. In countries where permits or licences are required from drug regulatory authorities and ministries of health before importation of drugs, data may be available from such sources. Customs services, in the process of clearing imports from the ports of entry, may collect data on drugs. However, the codes used by customs services are not detailed enough to capture all relevant information. National agencies responsible for the collection of excise duty can also provide information on the volume of production and on distribution of drugs from local manufacturers.

Data from these sources can generally be used to describe total quantities of specific drugs or drug groups, origins of supplies and type (i.e. branded or generic).

In the absence of a national mechanism for the direct capture of data on drug production or importation, wholesalers become an important source of information on drug acquisition. Such data are reliable insofar as wholesalers are the only legal entity able to import drugs. In some countries, medical, dental and veterinary practitioners, as well as pharmacists, can import pharmaceutical products. It is usually very difficult to collect comprehensive data from such sources even if there are regulatory requirements about submitting reports. Public sector procurement practices, however, have reasonable documentation but provide data only on that sector.

## PRACTICE SETTING DATA

*Prescribing data; dispensing data; drug use indicators; facility data (aggregate)*

Data from health facilities may be used to evaluate specific aspects of health provision and drug use and 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 adhere to established health care standards.

### 3.4.1 PRESCRIBING DATA

Prescribing data are usually extracted from outpatient and inpatient prescription forms. Such data may be easily retrieved where records are computerized and computerized data also facilitate trend analysis. In the absence of electronic databases, prescribing data are usually extracted from patient records or from patient intercept studies or retrieved at dispensing points.

Information that may be obtained from prescriptions includes patient demography, drug name, dosage form, strength, dose, frequency of administration and duration of treatment. Where diagnoses are noted on prescriptions, and particularly for inpatient prescription, it is possible to link drug use to indications. Trends in utilization for specific drugs and diseases can also be established. As an example, inpatient data may provide a link to empirical treatment of infections as opposed to treatment based on microbiological assessment. This may be achieved by extracting relevant data from the patient records, but requires that the records be of good quality.

Prescriptions are a good source of information for determining some of the indicators of drug use recommended by WHO including the:

- average number of drugs per prescription (encounter);
- percentage of drugs prescribed by generic name;
- percentage of encounters resulting in prescription of an antibiotic;
- percentage of encounters resulting in prescription of an injection;
- percentage of drugs prescribed from essential drugs list or formulary, and
- average drug cost per encounter.

Prescribing data allow the determination of the PDD which may differ from the DDD. While the DDD is based on the dosages approved in standard product characteristics with clinical outcome data from controlled clinical trials, the

PDD is variable and dependent on factors such as severity of illness, body weight, interethnic differences in drug metabolism and the prescribing culture of the health provider. Using DDDs enables comparison to be made between drug groups as the influences of prescribing culture and available dosage strengths are eliminated.

In some countries, it is a legal requirement that prescriptions dispensed by pharmacies and drug outlets are kept for a minimum period before disposal. Where these regulations are adhered to, prescription data may be obtainable from pharmacies. However, in many developing countries the rule is not generally followed. In countries where computerized records of prescribing data are kept, they may be readily retrievable depending on the depth of the database.

#### 3.4.2 DISPENSING DATA

Drug dispensing is a process that ends with a client leaving a drug outlet with a defined quantity of medication(s) and instructions on how to use it (them). The quantity of drugs dispensed depends on their availability. This information available from dispensers may include:

- drug(s) prescribed;
- dose(s) prescribed;
- average number of items per prescription;
- percentage of items prescribed that were actually supplied (an indicator of availability);
- percentage of drugs adequately labelled;
- quantity of medications dispensed; and
- cost of each item or prescription.

These data may be obtained from records kept at the drug outlet either in electronic or manual form.

#### 3.4.3 AGGREGATE DATA

A number of data sources within the health facility or hospital setting can provide aggregate data on drug utilization. These sources include procurement records, warehouse drug records, pharmacy stock and dispensing records, medication error records, adverse drug reaction records and patient medical records. These data sources

can be used to obtain information on various aspects of drug use including:

- the cost of individual drugs and classes of drug;
- the most frequently or infrequently used drugs;
- the most expensive drugs;
- the per capita consumption of specific products;
- comparisons of two or more drugs used for the same indication;
- the prevalence of adverse drug reactions;
- the prevalence of medication errors; and
- the percentage of the budget spent on specific drugs or classes of drug.

Aggregate data are often useful for comparing the utilization of a particular drug to that of other drugs and to utilization in other hospitals, regions or countries.

#### 3.4.4 OVER-THE-COUNTER AND PHARMACIST-PRESCRIBED DRUGS

Pharmacists and other drug outlet managers may prescribe over-the-counter preparations or pharmacist-prepared drugs that do not require prescription by a physician. Data on such medications may be difficult to obtain especially in environments with weak drug regulation and poor record keeping, but when such information is available from stock or dispensing records, it broadens the understanding of drug utilization patterns.

#### 3.4.5 TELEPHONE AND INTERNET PRESCRIBING

Physicians in certain countries may prescribe over the telephone. Prescribing and dispensing using the Internet also occurs, especially in developed countries. Most Internet prescriptions are for nutritional supplements and herbal preparations. However, as exemplified by sildenafil (Viagra®), other medicines are also increasingly being sold on the Internet. Innovative ways have to be devised to collect information on this type of transaction.

### 3.5 COMMUNITY SETTING DATA

[ *Household survey; compliance (adherence to treatment); drug utilization* ]

The drugs available in households have either been prescribed or dispensed at health facilities, purchased at a pharmacy (with or without a prescription) or are over-the-counter medications. The drugs may be for the treatment of a current illness or are left over from a previous illness. It is not uncommon for patients to adhere poorly to the instructions given for taking their dispensed medicines. Thus dispensing data and utilization data may not be equivalent because they have not been corrected for non-compliance.

Drug utilization by outpatients is best assessed by performing household surveys, counting left-over pills or using special devices that allow electronic counting of the number of times a particular drug is administered. Drug utilization by inpatients can be determined by reviewing treatment sheets or orders.

For both outpatients and inpatients, the data on the utilization of a particular drug can be aggregated for a defined population in DDDs. Using DDDs has the advantage of allowing comparison for example between inpatients and outpatients. Data on various dosage forms and generic equivalents of the same medication can also be aggregated.

### 3.6 DRUG USE EVALUATION

[ *Drugs and therapeutic committee; prospective evaluation; retrospective evaluation; criteria setting* ]

Drug use evaluation, sometimes referred to as drug utilization review, is a system of continuous, systematic, criteria-based drug evaluation that ensures the appropriate use of drugs. It is a method of obtaining information to identify problems related to drug use and if properly developed, it also provides a means of correcting the problem and thereby contributes to rational drug therapy.

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

- ensuring that drug therapy meets current standards of care
- controlling drug cost;
- preventing problems related to medication;
- evaluating the effectiveness of drug therapy; and
- identification of areas of practice that require further education of practitioners.

The problems to be addressed by drug use evaluation may be identified from any of the data described in section 3.4 (including prescription indicators, dispensing data and aggregate data). The main source of data for drug use evaluation is the patient records. An identifiable authoritative group, such as the drugs and therapeutic committee, usually carries out reviews of drug use in a hospital or health facility. This group has the responsibility for drawing up the guidelines, criteria, indicators and thresholds for the evaluation. Drug use evaluation may be based on data collected prospectively (as the drug is being dispensed or administered) or retrospectively (based on chart reviews or other data sources).

• Typical criteria reviewed in prospective studies include the following

- indications;
- drug selection;
- doses prescribed;
- dosage form and route of administration;
- duration of therapy;
- costs;
- therapeutic duplication;
- quantity dispensed;
- contraindications;
- therapeutic outcome
- adverse drug reactions; and
- drug interactions.



- In retrospective studies, the criteria reviewed include:
  - evaluation of indications;
  - monitoring use of high-cost medicines;
  - comparison of prescribing between physicians;
  - cost to patient;
  - adverse drug reactions; and
  - drug interactions.

It is possible to incorporate some of the above criteria into databases thus allowing drug experts to evaluate any items that do not meet established criteria. For meaningful results to be obtained from drug use evaluation a reasonable number of records need to be assessed. A minimum of 50 to 75 records per health care facility is considered adequate. However, the number of records sampled would depend on the size of the facility and the number of prescribers.

### 3.7 GENERAL READING

*How to investigate drug use in health facilities: Selected drug use indicators.* Geneva, World Health Organization, 1993 (unpublished document WHO/DAP/93.1; available on request from Department of Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva, 27, Switzerland).

### 3.8 EXERCISES

Examine the sources of data listed in the Worksheet. Imagine that you want to learn about the utilization of antibiotics in your country. In the spaces provided in the right-hand columns of the worksheet, write down (1) what kinds of useful data you might gather from each

source that could help you understand the situation, and (2) some possible advantages and/or limitations of each of the sources of data you have listed.

When evaluating the advantages and limitations of the data, consider the answers to the following questions:

- How relevant are the data for learning about antibiotics?
- How easy is it to collect these types of data in your country?
- How much will it cost to collect and process the data and how long will it take?
- How reliable are these data?

For example, from data from previous surveys, we might obtain the following useful information: historical utilization rates by facility or geographical area, and possibly utilization by type of antibiotic, health problem or age. The advantages of using historical survey data are that they have already been collected and carry no additional cost. However, their limitations include not being able to control exactly which data have been collected or from where, not knowing whether current practices reflect those of the past, and having no patient-specific or provider-specific information. It would also usually not be possible to find information on dosing of antibiotics.

**Worksheet for section 3.8**  
Sources of data on drug utilization

<b>Data source</b>	<b>Type of information available</b>	<b>Advantages and limitations</b>
Drug import records		
Drug supply to health facility Orders and/or delivery receipts		
Previous reports of surveys		
Pharmacy stock cards/ pharmacy ledger book		
Pharmacy sales receipts		
Large hospital or insurance databases		
Private drug outlet sales records		
Community or household surveys		
Drug manufacturing records		
Other sources		

*Pharmacoeconomics; types of cost; cost-minimization analysis; cost-effectiveness analysis; cost-benefit analysis; cost-utility analysis*

### 4.1 INTRODUCTION

Drug costs per se are important, as they account for a substantial part of the total cost of health care - typically 10-15% in developed countries and up to 30-40% in some developing countries. However, drug costs usually need to be interpreted in the context of the overall (net) costs to the health system. Drugs cost money to buy, but their use may also save costs in other areas. For example, the purchase of one specific type of drug may lead to reductions in the following:

- use of other drugs;
- the number of patients requiring hospitalization or in the length of stay in hospital;
- the number of doctor visits required;
- administration and laboratory costs compared with those incurred by using another drug to treat the same condition.

Assessing the true cost to a health system of using a specific drug will therefore require the cost of acquisition of the drug to be balanced against both any cost savings resulting from the use of that drug and the extra health benefits it may produce. On the other hand, costs may arise from adverse drug reactions both in the short- and particularly the long-term.

Assessing the value for money of using a drug requires the extra health benefits achieved to be weighed against the extra net cost. This comparison is usually expressed as an incremental cost-effectiveness ratio (ICER) which is the net incremental cost (costs minus cost offsets) of gaining an incremental health benefit over another therapy.

Concerns about the cost of medical care in general, and pharmaceuticals in particular, are currently being expressed by all health systems. There is a general focus on providing quality care within limited financial resources. Decision-makers are increasingly dependent on clinical economic data to guide policy formulation and implementation. Some of the concepts used in making such decisions include: cost-minimization, cost-effectiveness, cost-benefit, and cost-utility.

### 4.2 COST-MINIMIZATION ANALYSIS

Cost-minimization analysis is a method of calculating drug costs to project the least costly drug or therapeutic modality. Cost minimization also reflects the cost of preparing and administering a dose. This method of cost evaluation is the one used most often in evaluating the cost of a specific drug. Cost minimization can only be used to compare two products that have been shown to be equivalent in dose and therapeutic effect. Therefore, this method is most useful for comparing generic and therapeutic equivalents or «me too» drugs. In many cases, there is no reliable equivalence between two products and if therapeutic equivalence cannot be demonstrated, then cost-minimization analysis is inappropriate.

If a new therapy were no safer or more effective than an existing therapy (i.e. there is no incremental benefit), it would normally justify the same price as the existing therapy. An example would be the introduction of a new ACE inhibitor with essentially the same properties as existing members of the class; the price would be equivalent to that of the existing drug(s). This is often not as simple as it may seem, as it requires sound trial-based information on the doses of the two drugs required for equivalent efficacy. An alternative is to use the PDDs for the two drugs in the marketplace to determine the relative prices. This is a pragmatic approach, but assumes that the two drugs are actually used at equivalently effective doses, and this may not always be the case.

### 4.1 COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis involves a more comprehensive look at drug costs. While cost is measured in monetary terms, effectiveness is determined independently and may be measured in terms of a clinical outcome such as number of lives saved, complications prevented or diseases cured.

Cost-effectiveness analysis thus measures the incremental cost of achieving an incremental health benefit expressed as a particular health outcome that varies according to the indication for the drug. Examples of ICERs using this

approach are:

- the cost per extra patient achieving a 10 mm Hg fall in blood pressure;
- the cost per extra asthmatic patient achieving a reduction in oral corticosteroid use
- the cost per extra episode of febrile neutropenia avoided; or
- the cost per extra acute rejection episode avoided in patients with kidney transplants.

It is often difficult to make judgements about the relative value for money across a range of drug groups and health outcomes such as those in the examples given above.

#### 4.4 COST-UTILITY ANALYSIS

Cost-utility analysis is used to determine cost in terms of utilities, especially quantity and quality of life. This type of analysis is controversial because it is difficult to put a value on health status or on an improvement in health status as perceived by different individuals or societies.

Unlike cost-benefit analysis, cost-utility analysis is used to compare two different drugs or procedures whose benefits may be different.

Cost-utility analysis expresses the value for money in terms of a single type of health outcome. The ICER in this case is usually expressed as the incremental cost to gain an extra quality-adjusted life-year (QALY). This approach incorporates both increases in survival time (extra life-years) and changes in quality of life (with or without increased survival) into one measure. An increased quality of life is expressed as a *utility* value on a scale of 0 (dead) to one (perfect quality of life). An increased duration of life of one year (without change in quality of life), or an increase in quality of life from 0.5 to 0.7 utility units for five years, would both result in a gain of one QALY. This allows for easy comparison across different types of health outcome, but still requires value judgements to be made about increases in the quality of life (utility) associated with different health outcomes. The use of incremental cost-utility

ratios enables the cost of achieving a health benefit by treatment with a drug to be assessed against similar ratios calculated for other health interventions (e.g. surgery or screening by mammography). It therefore provides a broader context in which to make judgements about the value for money of using a particular drug.

#### 4.5 COST-BENEFIT ANALYSIS

Cost-benefit analysis is used to value both incremental costs and outcomes in monetary terms and therefore allows a direct calculation of the net monetary cost of achieving a health outcome. A gain in life-years (survival) may be regarded as the cost of the productive value to society of that life-year using, for example, the average wage. The methods for valuing gains in quality of life include techniques such as *willingness-to-pay*, where the amount that individuals would be willing to pay for a quality-of-life benefit is assessed. However, the techniques used to value health outcomes in monetary terms remain somewhat controversial, with the result that cost-benefit analysis is so far not widely used in pharmacoeconomic analyses.

Economic analyses such as those described above may be trial based or modelled. A trial based analysis uses the incremental benefits and use of resources in a clinical trial to calculate an ICER, but this may not be as relevant to the use of the drug as it would be in the marketplace. A modelled analysis is used to apply the benefits and use of resources to a local clinical situation, and to extend the time frame beyond that of a clinical trial. This is particularly important where the benefits of treatment may not be realized until some time in the future. Two examples are the avoidance of liver cancer or transplantation for patients with hepatitis C and the prolongation of life for hypertensive patients. Short-term surrogate outcome measures (clearance of virus and lowering of blood pressure, respectively) are used in clinical trials, and need to be translated by modelling into the longer-term outcomes, which are more relevant to patients and policy-makers.

#### 4.6 GENERAL READING

*How to investigate drug use in health facilities: Selected drug use indicators.* Geneva, World Health Organization, 1993 (unpublished document WHO/DAP/93.1; available on request from the Department of Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva, 27, Switzerland).

Schulman KA et al. Pharmacoeconomics: Economic evaluation of pharmaceuticals. In: Strom B. ed. *Pharmacoeconomics*, 3rd ed. Chichester, J Wiley, 2000.

#### 4.7 EXERCISES

##### 1. Comparison of antihypertensives

You are considering the use of a new alpha-antagonist for the treatment of hypertension. It is used once daily and you are told that it has been tested in trials against enalapril and losartan and it has been found to lower blood pressure to a similar extent to these agents. You already have prazosin on your subsidy list but the producers inform you that they have not carried out trials against prazosin. The approximate costs for a month's supply of the existing drugs are prazosin \$18, enalapril \$28 and losartan \$35. Beta-blockers and thiazide diuretics are also on your subsidy list at a cost of about \$8 for a month's supply but no trials of the new agent have been carried out against them. How would you approach the pricing of the new alpha-antagonist?

##### 2. Thrombolytics for acute myocardial infarction (a purely hypothetical exercise)

Congratulations! You have just been appointed as a member of the formulary committee of a large teaching hospital in Sydney, Australia. A key item on the agenda for the next meeting is a proposal to implement a management protocol for the treatment of acute myocardial infarction. You have been asked to evaluate the available evidence and advise to the committee as to which of two available drugs represents the more cost-effective choice.

The draft clinical management protocol currently proposes the use of the (hypothetical) thrombolytic drug Thrombase. A new drug,

Klotgon, has recently been brought to your attention. The two drugs have been compared in a large randomized trial in which the primary outcome of mortality was measured 30 days after randomization.

Outcomes in 100 patients	
No treatment	15 deaths
Thrombase	10 deaths
Klotgon	7 deaths
Drug cost per patient	
Thrombase	\$ 200
Klotgon	\$ 1000

You are also aware that the average survival time following non-fatal myocardial infarction is eight years.

Please answer the following questions. Be prepared to present your findings to the large group.

- If the hospital budget were unlimited, and if 1000 patients were to be treated, how many lives could be saved if patients were treated with Thrombase, compared with no treatment? How many could be saved with Klotgon, compared with no treatment?
- If the hospital's budget for purchasing thrombolytics were \$200 000, how many patients could be treated, and how many lives could be saved with each of the drugs, compared with no treatment at all?
- What is the *incremental cost per life saved*, for each of the thrombolytic agents, compared with no active treatment?
- What are the incremental cost-effectiveness ratios (ICERs), expressed as the *incremental cost per life-year gained*, for each of the thrombolytic agents, compared with no active treatment?
- What is the ICER for Klotgon compared to Thrombase?
- What will you recommend to the formulary committee?

Outcome	Low-molecular-weight heparin	Unfractionated heparin	P-value
Combined risk of death AMI <sup>1</sup> or unstable angina	318/1607 (19.8%)	364/1564 (23.3%)	0.016
Percutaneous revascularization (\$ 1390 per procedure)	236/1607 (14.7%)	293/1564 (18.7%)	0.002
Major bleeds	102/1569 (6.5%)	107/1528 (7.0%)	0.57
Minor bleeds	188/1580 (11.9%)	110/1528 (7.2%)	<0.001

### 3. Unfractionated heparin versus low-molecular-weight heparin

Because of your valuable contribution to the development of a cost-effective treatment protocol for acute myocardial infarction, you have been retained as a member of the formulary committee of the above-mentioned hospital. An agenda item for consideration at your committee's next meeting concerns a recommendation, from a very pleasant pharmaceutical company representative, that you replace unfractionated heparin with a low-molecular-weight heparin in the management of patients with unstable coronary artery disease. She very kindly gives you a summary of some data from a clinical trial published in the *New England Journal of Medicine*. The outcomes were reported 30 days after randomization.

You decide to investigate the costs of acquiring and monitoring treatment with the two drugs and note the following:

Item	Low-molecular-weight heparin	Unfractionated heparin
Monthly drug costs (\$)	\$72.20	\$27.09
Monthly cost monitoring	none	5 tests/patient of
anticoagulant effect		@ \$12.40 per test

<sup>1</sup> Acute myocardial infarction

Please answer the following questions. Be prepared to present your findings to a large group.

- Calculate the relative risk of the combined (triple) end-point in patients who received low-molecular-weight heparin compared with those who received unfractionated heparin.
- Calculate the risk difference and the number of patients who need to be treated to prevent a single event with low-molecular-weight heparin compared with unfractionated heparin.
- Calculate the ICER for the main clinical outcome with low-molecular-weight heparin, compared with unfractionated heparin using drug costs only.
- Recalculate the ICER for the main clinical outcome with low-molecular-weight heparin, compared with unfractionated heparin including the costs of monitoring treatment with heparin.

### 4. Celecoxib versus diclofenac

A representative from a very supportive pharmaceutical company addressed your medical staff during a Saturday seminar last week. She gave an interesting presentation on the comparative safety of some well-known anti-inflammatory preparations. At the formulary meeting this week, the head of your rheumatology department is planning to propose adding celecoxib, a COX-

2 inhibitor, to the hospital formulary in place of NSAIDs. He intends to argue that the hospital will save a lot of money by avoiding the complications associated with NSAIDs such as peptic ulcers. This item was placed on the agenda of

the committee as a late submission, so you decide to review the evidence and prepare yourself for the discussion. You find the following results of a clinical trial reported in the *Lancet*.

<b>Mean (SD) arthritis assessment results at week 24</b>				
Primary assessments	Celecoxib		Diclofenac	
	Baseline	Week 24	Baseline	Week 24
Physician's assessment <sup>a</sup>	2.9 (0.7)	2.6 (0.8)	3.0 (0.8)	2.6 (0.8)
Patient's assessment <sup>a</sup>	3.0 (0.8)	2.7 (0.9)	3.1 (0.8)	2.8 (0.9)
No. of tender/painful joints	20.3 (14.4)	14.5 (14.1)	21.7 (14.4)	16.4 (14.7)
No. of swollen joints	14.9 (10.2)	10.7 (10.1)	14.3 (9.9)	10.4 (10.0)

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The following adverse event data were also reported.

<b>Frequency of peptic ulceration and related complications</b>			
	Celecoxib (n = 212)	Diclofenac (n = 218)	P-value
<i>Patients in whom erosion, ulcer or both were detected</i>			
Gastric	38 (18%)	74 (34%)	<0.001
Duodenal	11 (5%)	23 (11%)	<0.009
<i>Ulcer incidence by Helicobacter pylori status</i>			
Positive serological test	7/93 (8%)	19/87 (22%)	NS
Negative serological test	1/97 (1%)	10/100 (10%)	NS
<i>Ulcer frequency by concomitant corticosteroid use</i>			
Corticosteroid use	2/80 (3%)	12/102 (12%)	NS
No corticosteroid use	6/132 (5%)	21/116 (18%)	NS
NS: not significant.			

<sup>a</sup>Independent assessments, graded from 1 (very good: symptom-free with no limitation of normal activities) to 5 (very poor: very severe symptoms that are intolerable, and inability to carry out all normal activities).

From your research you also know that:

- One per cent of patients with endoscopic damage are hospitalized with gastrointestinal bleeding.
- The cost of hospitalization for gastrointestinal bleeding is \$1434/patient.
- Ten per cent of patients admitted with gastrointestinal bleeding die.
- The cost of celecoxib for 60 x 100 mg tablets is \$50.
- The usual dose of celecoxib is 200 mg bd.
- The cost of diclofenac is \$11.60 for 50 x 50 mg tablets; \$14.35 for 100 x 25 mg tablets.
- The usual dose of diclofenac is 50 mg-75 mg bd.
- Answer the following questions. Be prepared to present your findings to a large group.

a. Calculate the relative risk for peptic (i.e. gastric or duodenal) ulcers in the patients who received celecoxib compared with those who received the NSAID diclofenac.

b. Calculate the risk difference and the number of patients who have to be treated to prevent a single event with celecoxib, as compared with the NSAID.

- c. Calculate the ICER for the main clinical outcome with celecoxib, compared with the NSAID, using drug costs only.
- d. Recalculate the ICER for the main clinical outcome with celecoxib, compared with the NSAID, including the costs of treatment of gastrointestinal bleeding.

### 5. Oral montelukast versus an inhaled steroid

A community-driven asthma awareness group has donated 10 cartons of montelukast tablets for adults treated in your hospital's asthma clinic. They feel strongly that this product should be made available since, according to the medical adviser of the sponsoring company, it is much more effective and much easier to use than the usual «puffers». As this product is fairly new, the formulary committee has been asked to comment on its effectiveness. Since the asthma unit will prepare a submission for including it in the hospital formulary after the supply of donated drugs is exhausted, you have been asked to comment on the comparative cost-effectiveness of the drug. You begin your assessment by considering the following results at 22 weeks after the baseline assessment.

End-point	Placebo	Beclometasone	Montelukast
Percentage change *FEV <sub>1</sub>	0.7 [-2.3, 3.7]	13.1 [10.1, 16.2]	7.4 [4.6, 10.1]
Change in daytime asthma symptom score	-0.17 [-0.3, -0.05]	-0.62 [-0.75, 0.49]	-0.41 [-5.3, -0.29]
Percentage change in total daily $\epsilon$ -agonist use	0.0 [-8.3, 8.3]	-40.0 [-48.5, -31.5]	-23.9 [-31.4, -16.5]
Change in morning PEFr [l/min]	0.8 [-7.1, 8.6]	39.1 [31.0, 47.1]	23.8 [16.6, 30.9]
Change in evening PEFr [l/min]	0.3 [-7.3, 8.0]	32.1 [24.2, 39.9]	20.8 [13.8, 27.8]
Change in nocturnal awakenings [nights per week]	-0.5 [-0.9, -0.1]	-2.4 [-2.8, -2.0]	-1.7 [-2.07, 1.3]
Change in eosinophil count [cells x 10 <sup>3</sup> / $\mu$ l]	-0.02 [-0.07, 0.03]	-0.07 [-0.12, -0.02]	-0.08 [-0.12, -0.03]
Percentage of patients with asthma attacks	27.3	10.1	15.6

Values are mean [95% CI]. \*FEV<sub>1</sub> = forced expiratory volume in one second; PEFr = peak expiratory flow rate



The costs of the two drugs are:

- Beclometasone: Australian \$26 for 28 days of treatment;
- Montelukast: Australian \$70 for 28 days of treatment.

Please answer the following questions. Be prepared to present your findings to a large group.

- a. You wish to compare montelukast with beclometasone. Which outcome(s) will you use for the comparison? Why?
- b. Calculate the ICER for the main clinical outcome.
- c. Which is the better drug? Why?

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 standardized 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 these 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 systems for monitoring cross-national patterns of antibacterial utilization to aid work against bacterial resistance.

### 5.1 DIFFERENT CLASSIFICATION SYSTEMS

*ATC classification; AT classification; EPhMRA; IMS; WHO Collaborating Centre for Drug Statistics Methodology*

Drugs can be classified in different ways according to:

- their mode of action;
- their indications; or
- their chemical structure.

Each classification system will have its advantages and limitations and its usefulness will depend on the purpose, the setting used and the user's knowledge of the methodology.

Comparisons between countries may require a classification system different from that needed for 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» (AT) classification 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 modifies and extends the EPhMRA system to include a therapeutic/pharmacological/chemical subgroup as the fourth level and the chemical substance as the fifth level (see, for example, the classification of glibenclamide in the box below).

The ATC classification is also the basis for the classification of adverse drug reactions used by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden ([www.who-umc.org](http://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 WHO for use in international comparisons. The EPhMRA classification system is used worldwide by IMS for providing market research statistics to the pharmaceutical industry. It should be emphasized that the many technical differences between the EPhMRA classification and the ATC classification mean that data prepared using the two classification systems are not directly comparable.

In 1996, WHO recognized the need to develop the ATC/DDD system from a European to an international standard in drug utilization studies. The European WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway, which is responsible for coordinating the use of the methodology, was then linked to WHO Headquarters in Geneva. This was intended to assist WHO in its efforts to ensure universal access to essential drugs and to stimulate rational use of drugs particularly in developing countries.

### 5.2 THE ATC CLASSIFICATION SYSTEM

*Structure; coding principles; therapeutic use; pharmaceutical formulations; strengths*

The ATC classification system divides the drugs into different groups according to the organ or

system on which they act and according to their chemical, pharmacological and therapeutic properties.

Drugs are classified in groups at five different levels. The drugs are divided into 14 main groups (first level), with two therapeutic/pharmacological subgroups (second and third levels). The fourth level is a therapeutic/pharmacological/chemical subgroup and the fifth level is the chemical substance. The second, third and fourth levels are often used to identify pharmacological subgroups when these are considered to be more appropriate than therapeutic or chemical subgroups.

The complete classification of glibenclamide (see box below) illustrates the structure of the code.

A	Alimentary tract and metabolism (first level, main anatomical group)
A10	Drugs used in diabetes (second level, main therapeutic group)
A10B	Oral blood-glucose-lowering drugs (third level, therapeutic /pharmacological subgroup)
A10B B	Sulfonamides, urea derivatives (fourth level, chemical/therapeutic /pharmacological subgroup)
A10B B01	Glibenclamide (fifth level, subgroup for chemical substance)

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

Medicinal products are classified according to the main therapeutic use of their main active ingredient, on the basic principle of assigning only one ATC code for each pharmaceutical formulation (i.e. similar ingredients, strength and pharmaceutical form).

A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses. Two examples of this are given below:

- Sex hormones in certain dosage forms or strengths are used only in the treatment of cancer and are thus classified under L02 - Endocrine therapy. The other dosage forms and strengths are classified under G03 - Sex hormones and modulators of the genital system.
- Bromocriptine is available in different strengths. The low-dose tablets are used as prolactin inhibitors and are classified in G02 - Other gynaecologicals. Bromocriptine tablets in higher strengths are used to treat Parkinson disease and are classified in N04 - Anti-Parkinson drugs.

Different formulations with different indications may also be given separate ATC codes, for example prednisolone is given several ATC codes because of the different uses of the different formulations (see box below).

A07E A01	Intestinal anti-inflammatory agents ( <i>enemas and rectal foams</i> )
C05A A04	Antihaemorrhoidals for topical use ( <i>rectal suppositories</i> )
D07A A03	Dermatological preparations ( <i>creams, ointments, lotions</i> )
H02A B06	Corticosteroids for systemic use ( <i>tablets, injections</i> )
R01A D02	Nasal decongestants ( <i>nasal spray, drops</i> )
S01B A04	Ophthalmologicals ( <i>eye drops</i> )
S02B A03	Otologicals ( <i>ear drops</i> )

The ATC system is not strictly a therapeutic classification system. At all ATC levels, ATC codes can be assigned according to the pharmacological properties of the product. Subdivision on the basis of mechanism of action will understandably be rather broad, since a very detailed classification

cation of this kind would result in having only one substance per subgroup, which is better avoided (e.g. in the case of antidepressants). Some ATC groups are subdivided into both chemical and pharmacological groups (e.g. ATC group J05A - Agents affecting the virus directly). If a new substance fits in both a chemical and pharmacological fourth level, the pharmacological group is normally chosen.

Substances classified as having the same ATC fourth level should not be considered as pharmacotherapeutically equivalent since the profiles for their mode of action, therapeutic effects, drug interactions and adverse drug reactions may differ.

As the drugs available and their uses are continuously changing and expanding, regular revisions of the ATC system are necessary. An important principle is to keep the number of alterations to a minimum. Before alterations are made, any potential difficulties arising for the users of the ATC system are considered and related to the benefits that would be achieved by the alteration. Changes to the ATC classification would be made when the main use of a drug had clearly changed, and when new groups are required to accommodate new substances or to improve the specificity of the groupings.

Because the ATC system separates drugs into groups at five levels (described above), statistics on drug utilization grouped at the five different levels can be provided. The information available ranges from figures showing total use of all drug products classified e.g. in main group C - Cardiovascular system (first level), to figures for the different subgroups (i.e. second, third and fourth level) to figures for the use of the separate substances.

More detailed information can be obtained at the lower (i.e. the fourth and fifth) levels. The higher levels are used if comparison of drug groups is the aim of a study (see Fig. 5). This gives a better overview and trends in drug use related to different therapeutic areas can easily be identified.

### 5.3 AMBIVALENCE TOWARDS AN INTERNATIONAL CLASSIFICATION SYSTEM

All international standards demand compromises and a drug classification system is no exception to this rule. Drugs may be used for two or more equally important indications, and the main therapeutic use of a drug may differ from one country to another. This will often result in several

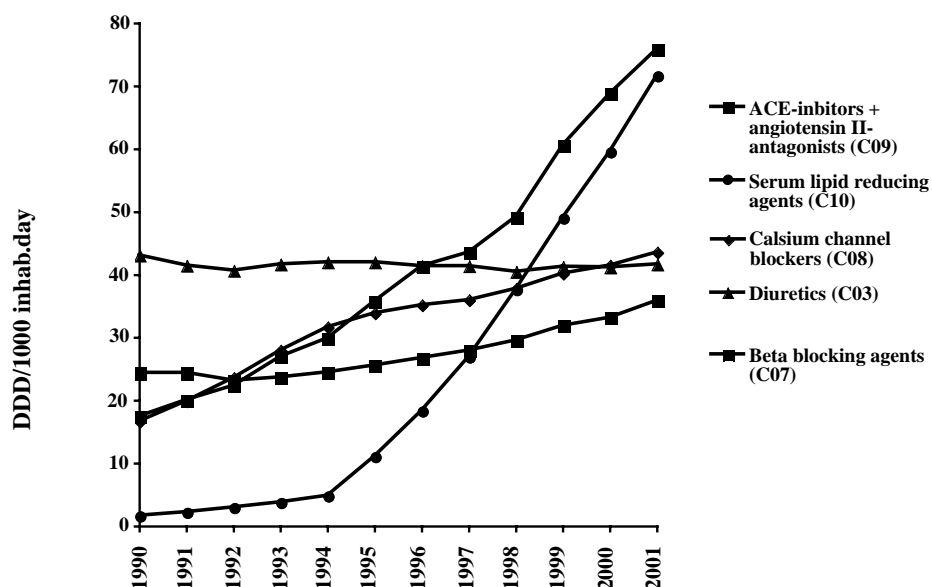


Figure 5 Total sales of drugs used in cardiovascular disorders in Norway 1990-2001. ATC/DDD version 2002

possible alternatives for classification, and a decision has to be made regarding the main use. Countries using a drug in a different way from that indicated by the ATC classification may not wish to adopt the ATC classification but prefer to develop national classification systems. However, national traditions have to be weighed against the opportunity to introduce a methodology that permits valid international comparisons of drug utilization. Indeed, there are now many examples where an enthusiastic application of the ATC/DDD methodology has been instrumental in stimulating national research in drug utilization and in developing an efficient drug control system.

#### 5.4 IMPLEMENTATION OF THE ATC/DDD METHODOLOGY

[ *National drug register; dynamic system; different versions* ]

As soon as the decision to introduce the ATC/DDD methodology is taken, it is essential to realize that its proper use inevitably includes an important and time-consuming first step. Each product has to be connected to the appropriate ATC code and DDD (see chapter 6). The linkage between the national drug register and ATC/DDDs has to be ascertained by persons with proper knowledge of the methodology. Experience has shown that in many countries, health authorities, health policy-makers and researchers have not always allocated adequate resources to this important initial step. Another problem is that some users seem to be unaware that the ATC/DDD methodology is a dynamic system to which changes are made continually. This has resulted in several different versions of the ATC/DDD system being used at the same time, sometimes even within the same country.

It is important to realize that adopting the ATC/DDD classification of drugs requires resources and the necessary competence to carry out the work of allocating ATC codes to the products. If possible, this work should be done on a

national basis to secure consistent use of the methodology within a country. As described in the general introduction, the same substance may have several different ATC codes depending on the application form and, to some extent, even the strength. For combination products, specific guidelines have been established for allocating ATC codes. Allocating DDDs to the products necessitates many of the same considerations as the allocation of the ATC code. However, in order to link the drug list with sales figures or prescription figures to obtain drug utilization statistics, it is necessary to make appropriate calculations such as the number of DDDs per drug package.

Finally, a given country will nearly always have medicines and combination products for which no ATC codes or DDDs exist. In these cases, it is important to consult the WHO Collaborating Centre for Drug Statistics Methodology in Oslo and request new ATC codes and DDDs. Once ATC codes and DDDs have been linked to the national drug lists, it is necessary to update the drug list regularly in accordance with the annual updates of the ATC/DDD system.

The publication *Guidelines for ATC Classification and DDD Assignment* (see General reading) gives the information necessary for allocating ATC codes and DDDs at a national or local level. All officially assigned ATC codes and DDDs are listed in the *ATC Index with DDDs* (see General reading), a publication that is also available in electronic format and is updated every year. Training courses in the ATC/DDD methodology are arranged annually in Norway and from time to time in other countries. Further information is available on the web site of the WHO Collaborating Centre for Drug Statistics Methodology at <http://www.whocc.no>.

#### 5.5 GENERAL READING

*Guidelines for ATC classification and DDD Assignment*. Oslo, Norway, WHO Collaborating Centre for Drug Statistics Methodology, 2003.

*ATC Index with DDDs*. Oslo, Norway, WHO Collaborating Centre for Drug Statistics Methodology, 2003.

Capellà D. Descriptive tools and analysis. In: Dukes MNG ed. *Drug utilization studies, methods and uses*. Copenhagen, WHO Regional Office for Europe, 1993 (WHO Regional Publications, European Series, No. 45), 55-78.

Rønning M et al. Different versions of the anatomical therapeutic chemical classification system and the defined daily dose - are drug utilization data comparable? *European Journal of Clinical Pharmacology*, 2000, 56:723-727.

Rägo L. Estonian regulatory affairs. *Regulatory Affairs Journal*. 1996, 7:567-573.

## 5.6 EXERCISES

1. «Neurol» is a major tranquillizer belonging to the butyrophenone group of antipsychotics. The only ATC code for this substance at present is in N01A X. The parenteral formulations of Neurol are used for various indications e.g. in anaesthesia, as antiemetics and in the

treatment of schizophrenia. The oral formulations of Neurol are, however, used mainly in the treatment of schizophrenia.

Discuss whether it would be appropriate to assign an additional ATC code in N05 for oral formulations of Neurol.

2. Lisuride has been assigned two codes in the ATC classification system: G02CB02 (*Prolactin inhibitors*) and N02CA07 (*Antimigraine preparations*). Lisuride preparations in high strengths (e.g. tablets of 0.2 mg) are classified in G02CB. The recommended dose range for prolactin inhibition is 0.1-0.2 µg x 3. Low-strength preparations (e.g. tablets of 25 µg) are classified in N02CA. The recommended dose range for treatment of migraine is 25 mg x 3.

Lisuride is also used for the treatment of parkinsonism. The recommended dose range for this indication is 0.2-0.6 mg daily.

Discuss whether it would be appropriate to assign an additional ATC code for lisuride in N04.

## CHAPTER 6: DRUG UTILIZATION METRICS AND THEIR APPLICATIONS

### 6.1. THE CONCEPT OF THE DEFINED DAILY DOSE (DDD)

*Definition; DDDs per 1000 inhabitants per day; DDDs per 100 bed-days; DDDs per inhabitant per year*

The historical development of the concept of the defined daily dose (DDD) and its early applications are described in the Preface.

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

It should be emphasized that the DDD is a unit of measurement and does not necessarily correspond to the recommended or prescribed daily dose (PDD). Doses for individual patients and patient groups will often differ from the DDD as they must be based on individual characteristics (e.g. age and weight) and pharmacokinetic 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 seldom prescribed, because it is an average of two or more commonly used dose sizes.

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

These terms are explained below.

#### *DDD per 1000 inhabitants per day*

Sales or prescription data presented in DDDs per 1000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs. As an example, the figure 10 DDDs

per 1000 inhabitants per day indicates that 1% of the population on average might receive a certain drug or group of drugs daily. 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 the denominator. Usually the general utilization is calculated for the total population including all age groups, but some drug groups have very limited use among people below the age of 45 years. To correct for differences in utilization 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 the denominator.

#### *DDD per 100 bed-days*

The DDDs per 100 bed-days may be applied when drug use by inpatients is considered. The definition of a bed-day may differ between hospitals or countries, and bed-days should be adjusted for occupancy rate. The same definition should be used when performing comparative studies. As an example, 70 DDDs per 100 bed-days of hypnotics provide an estimate of the therapeutic intensity and suggests that 70% of the inpatients might receive a DDD of a hypnotic every day. This unit is quite useful for benchmarking in hospitals.

#### *DDD per inhabitant per year*

The DDDs per inhabitant per year may give an estimate of the average number of days for which each inhabitant is treated annually. For example, an estimate of five DDDs per inhabitant per year indicates that the utilization is equivalent to the treatment of every inhabitant with a five-day 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.

## 6.2 PRESCRIBED DAILY DOSE AND 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 studies of prescriptions or medical or pharmacy records. It is important to relate the PDD to the diagnosis on 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.

For drugs where the recommended dosage differs from one indication to another (e.g. the antipsychotics), it is important to link the diagnosis to the PDD. Pharmacoepidemiological information (e.g. on sex, age and whether therapy is mono- or combined) is also important in order to interpret a PDD.

The PDD can vary according to both the illness treated and national therapeutic traditions. For instance, for the anti-infectives, PDDs vary according to the severity of the infection treated. The PDDs also vary substantially between different countries, for example, PDDs are often lower in Asian than in Caucasian populations. The fact that PDDs may differ from one country to another should always be considered when making international comparisons.

It should be noted that the PDD 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. the consumed daily dose).

## 6.3 OTHER UNITS FOR PRESENTATION OF VOLUME

Common physical units (e.g. grams, kilograms and litres), numbers of packages or tablets and numbers of prescriptions are also used for quan-

tifying drug utilization, but have certain disadvantages (see below). These units can be applied only when the use of a single drug or of well-defined products is evaluated. Problems arise, however, when the utilization of whole drug groups is considered.

### *Grams of active ingredient*

If utilization is given in terms of grams of active ingredients, drugs with low potency will account for a larger fraction of the total than drugs with high potency. Combined products may also contain different amounts of active ingredients from plain products, and this difference will not be reflected in the figures.

### *Number of tablets*

Counting numbers of tablets does not reflect the variations in strengths of tablets, with the result that low-strength preparations contribute relatively more than high-strength preparations to the total numbers. Also, short-acting preparations will often contribute more than long-acting preparations.

### *Numbers of prescriptions*

Numbers of prescriptions do not accurately reflect total use, unless total quantities of drugs per prescription are also considered. However, counting of prescriptions is valuable in measuring the frequency of prescriptions and in evaluating the clinical use of drugs (e.g. diagnosis and dosages used).

Although they are useful in making national comparisons it should be noted that none of these volume units is usually applicable in cross-national comparisons, as was pointed out during the 1969 WHO symposium in Oslo.

## 6.4 COST

Drug use can be expressed in terms of costs (e.g. national currency). Cost figures are suitable for an overall analysis of expenditure on drugs. International comparisons based on cost parameters can be misleading and have limited value in the evaluation of drug use. Price differences between alternative preparations and different



national cost levels make the evaluation difficult. Long-term studies are also difficult due to fluctuations in currency and changes in prices.

When cost data are used, an increase in the use of cheaper drugs may have little influence on the total level of expenditure on drugs, while a shift to more expensive drugs is more readily noticed.

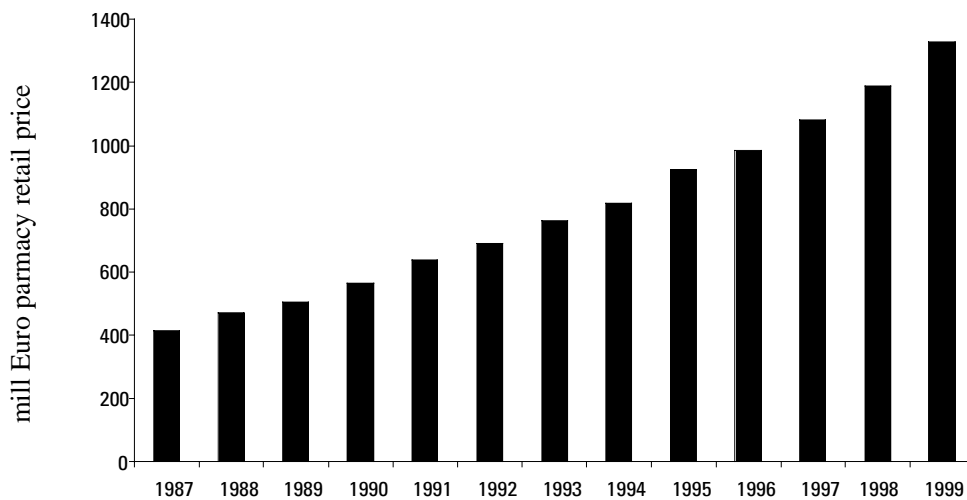
The trends in drug use measured in cost may therefore look very different from the same drug use measured in DDDs. As an example, the total drug use in Norway from 1987-1999 measured in cost (Euros) and in DDDs is shown in Figs 6 and 7.

## 6.5 GENERAL READING

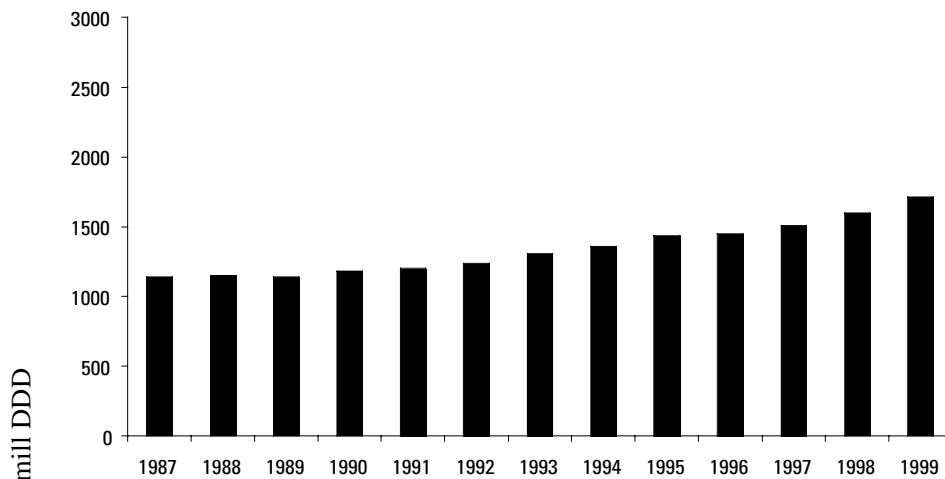
*Consumption of drugs. Report of a symposium in Oslo, 1969.* Copenhagen, WHO Regional Office for Europe, 1970 (EURO 3102).

*Studies in drug utilization: methods and applications.* Copenhagen, WHO Regional Office for Europe 1979 (Regional Publications European Series No.8).

Bergman U et al. Auditing hospital drug utilization by means of defined daily doses per bed-day. A methodological study. *European Journal of Clinical Pharmacology*, 1980, 17:183-187.



**Figure 6** Total sales of drugs in Norway in millions of Euros 1987-1999



**Figure 7** Total sales of drugs in Norway in millions of DDDs 1987-1999

Baksaas I. Patterns in drug utilization - national and international aspects: antihypertensive drugs. *Acta Medica Scandinavica*, 1984, suppl. 683:59-66.

Lee D, Bergman U. Studies of drug utilization. In: Strom B ed. *Pharmacoepidemiology*, 3rd ed. Chichester, J Wiley, 2000:463-481.

## 6.6 EXERCISES

1. Assign DDDs for the two antibacterials below according to the following dose recommendations.

**Substance A:** 500 mg on first day, then 250 mg daily; duration of treatment 14 days.

**Substance B:** 500 mg on first day, then 250 mg daily; duration of treatment five days.

2. The DDD for budesonide inhalation powder was changed from 0.3 mg to 0.8 mg in 1991. The following sales figures from Norway for budesonide inhalation powder are found in two different books on drug statistics.

1990 9.6 DDDs /1000 inhabitants/day  
(DDD = 0.3 mg)

1994 11.6 DDDs /1000 inhabitants/day  
(DDD = 0.8 mg)

Comment on the comparability of these figures. Discuss how to best present the sales figures from these two years in the same article.

3. Annual sales figures given in millions of DDDs are:

	Substance A	Substance B
1988	1.7	21.6
1996	9.1	9.9

Total number of inhabitants: 4 million

Calculate total number of four-day courses of substance A sold per year and the equivalent number of courses per inhabitant.

Calculate total number of eight-day courses of substance B sold per year and the equivalent number of courses per inhabitant.

## Chaper 2 - Types of drug use information

### 2.1. Amoxicillin

The use of a drug expressed as DDD/1000 population/day is derived by calculating the overall amount of a drug being used over a specified period of time (e.g. a year) and dividing this by the DDD multiplied by the population and the number of days in the period.

$$\text{DDD/1000 population/day} = \frac{\text{Amount used in 1 year (mg)} * 1000}{\text{DDD(mg)} \times \text{population} \times 365(\text{days})}$$

The amount used is a function of the number of prescriptions, the number of tablets or capsules per prescription and the dose size of the tablets or capsules.

An understanding of the above allows the following hypotheses about the reasons for increased use to be generated and tested.

#### *Hypothesis 1*

##### ***The number of prescriptions per year has increased.***

The information needed to test this hypothesis would be prescription numbers per year adjusted for population changes over the study period. Remember that the DDD/1000 population/day is corrected for population changes. Another way of addressing this hypothesis for a drug mainly used acutely in short courses would be to obtain data expressed as the number of amoxicillin treatment courses/1000 population/year.

If the prescription rate has increased, questions could be asked about the reasons for this.

Have the indications changed?

This would require data over time on the indications for which amoxicillin is used.

Has there been increased promotion for example, to introduce a new brand? This would require a survey of promotional materials over time.

#### *Hypothesis 2*

##### ***The amount of amoxicillin per treatment course has increased.***

This might be the result of an increase in the average length of the course and/or an increase in the average PDD. The first possibility could be addressed by a survey of prescribers to find out about the length of treatment courses, or a survey of prescriptions to calculate the duration of treatment by dividing the PDD by the total quantity prescribed. To obtain the PDD, a prescription survey would be required, either designed for this purpose or making use of data from ongoing surveys such as those conducted by IMS.

### 2.2. Antidepressant use

Both **use** and **cost** have been noted to increase over time. The types of data required to determine the reasons for increased **use** are similar to those suggested in answer to question 1 with some differences. In this case, the data on the use of all the antidepressants have been aggregated so the data on the use of the individual agents and groups (TCAs, SSRIs and monoamine oxidase (MAO) inhibitors) will need to be disaggregated. In looking at the relative use of drugs or drug groups, it may be necessary to use both DDD/1000 population/day and prescrip-

tion numbers. To interpret the data fully, it may be necessary to determine the PDDs for each drug or drug group. If the relationship between DDD and PDD differs for the different drugs, the trends based on DDD/1000 population/day may be misleading. For example, the use of the SSRIs and moclobemide may have increased, while only a small decrease in TCA use has occurred. This would have increased total antidepressant use with a multiplier effect on cost as the SSRIs and moclobemide are patented and much more expensive than the older drugs. If this is what has occurred a number of questions can be asked.

- Is the incidence or prevalence of depression in the community increasing?
- Is there increased awareness of depression by doctors and patients resulting in a higher proportion of patients with depression being treated?
- If so, is this the result of government educational initiatives, or pharmaceutical promotion aimed at case-finding and enhancement of compliance.
- Are there changes in the doses being used or in the duration of treatment?
- Has there been a change in the indications for which antidepressant drugs are used?
- For example, has there been an increase in their use for the treatment of obsessive-compulsive disorder, panic attacks or chronic pain?

Different types of data will be required to answer some of these questions and special surveys will have to be designed and carried out. Some information (on indications, dose and duration of treatment) may be available from ongoing prescriber surveys carried out either by academic units or by commercial sources such as IMS. Data on the incidence and prevalence of depression may be available from government disease registries or similar sources. Qualitative studies may need to be designed and carried out to determine for example, the degree of awareness of depression as a problem and the sources that have been used to obtain information about depression and its treatment.

Cost is a function of price and volume. The issue of volume has been addressed above. A full assessment of the reasons for cost increases will require information on the price trends for the drugs over time.

*Questions about changes in utilization of a drug or drug group over time require a number of different types and sources of data.*

## **Chaper 4 - Economic aspects of drug use (pharmacoeconomy)**

### **4.1. Comparison of antihypertensives**

The goal of treating hypertension in terms of health outcomes is to prolong life by preventing cardiovascular events and target organ damage. This is achieved by lowering blood pressure to a range where absolute cardiovascular risk is essentially reduced to the population level. The reduction in blood pressure is a surrogate outcome measure, but is accepted by most regulatory authorities for registration purposes. All the drug groups lower blood pressure to approximately the same extent. Outcome studies are available for diuretics, beta-blockers and for the ACE inhibitors, but not for the alpha-antagonists. In terms of subsidy listing, a principle should be that, to achieve a price premium, a new drug should have demonstrated an increased benefit in terms of health outcomes.

The company argues that this is a new innovative treatment that has been shown to be equiva-

lent to losartan and they therefore demand a price equivalent to the A2 antagonists.

You reply that this is just another alpha-antagonist and it should therefore be compared with prazosin.

The company states that there are no head-to-head trials of the new agent against prazosin (they have not done any trials and have no intention of doing so) and therefore no evidence on which to base a comparison. They argue the new agent should be compared with the ACE inhibitors and A2 antagonists where there are good comparative data.

You reply that the lack of data comparing the new agent with prazosin is their problem, and that if they want a higher price they should do the studies to demonstrate a health outcome benefit over prazosin. Indeed, you wonder why prazosin has a price premium over the diuretics and beta-blockers and whether this should be reviewed to determine whether the higher price is justified.

The company now argues that the new innovative drug has a longer half-life than prazosin so that it can be administered once a day compared to twice a day for prazosin. It would therefore improve compliance which is a very important consideration in treating hypertension.

You reply that the company has not demonstrated that the once-daily dose leads to improved compliance or health outcomes and there is little evidence to support this supposition. A small premium might be considered for the extra convenience for patients who are taking a life-long treatment when they are essentially without symptoms.

The company decides not to proceed with the marketing of the new drug. Who is right in this story? What price would **you** offer for this drug? Are you concerned that it won't be available?

#### 4.2. *Thrombolytics for acute myocardial infarction*

a. Of 1000 patients treated with a placebo, 150 will die.

Of 1000 patients treated with Drug A (Thrombase), 100 will die, therefore 50 lives will be saved.

Of 1000 patients treated with Drug B (Klotgon) 70 will die, therefore 80 lives will be saved.

##### b. *Treatment with Thrombase*

If the budget is \$200 000 and the cost of treatment is \$200 per patient (\$2000/\$200), 1000 patients could be treated and 50 lives saved (see question 1 above).

##### *Treatment with Klotgon*

If the budget is \$200 000 and the cost of treatment is \$1000 per patient (\$200 000/\$1000), 200 patients could be treated and  $80 \times 200/1000 = 16$  lives could be saved.

c. If 1000 patients are treated with Thrombase, 50 lives are saved.

ICER (Thrombase versus placebo for 1000 patients) =  $\frac{(1000 \times \$200 - 1000 \times \$0)}{50 \text{ lives saved}}$

=  $\frac{\$200\,000}{50} = \$4000$  per life saved

If 1000 patients are treated with Klotgon, 80 lives are saved.

ICER (Klotgon versus placebo for 1000 patients)

$$= \frac{(1000 \times \$1000 - 1000 \times \$0)}{80 \text{ lives saved}} = \frac{\$1\,000\,000}{80} = \$12\,500 \text{ per life saved.}$$

**d.** If 1000 patients are treated with Thrombase, 50 lives are saved. Assuming an increase in survival time of eight years per patient,  $50 \times 8 = 400$  life-years are gained.

ICER (Thrombase versus placebo for 1000 patients)

$$= \frac{(1000 \times \$200 - 1000 \times \$0)}{400 \text{ life-years}} = \frac{\$200\,000}{400} = \$500 \text{ per life-year gained.}$$

If 1000 patients are treated with Klotgon, 80 lives are saved. Assuming an increase in survival time of eight years per patient,  $80 \times 8 = 640$  life-years are gained.

ICER (Klotgon versus placebo for 1000 patients)

$$= \frac{(1000 \times \$1000 - 1000 \times \$0)}{640 \text{ life-years}} = \frac{\$1\,000\,000}{640} = \$1\,562.50 \text{ per life-year gained.}$$

**e.** If 1000 patients are treated with Thrombase, 50 lives are saved; if 1000 patients are treated with Klotgon, 80 lives are saved; therefore, 30 lives are saved by treatment with Klotgon rather than Thrombase.

Assuming an increase in survival time of eight years per patient,  $30 \times 8 = 240$  life-years are gained.

ICER (Klotgon versus Thrombase for 1000 patients)

$$= \frac{(1000 \times \$1000 - 1000 \times \$200)}{240 \text{ life-years}} = \frac{\$800\,000}{240} = \$3\,333 \text{ per life-year gained.}$$

#### 4.3. Unfractionated heparin versus low-molecular-weight heparin

**a.** Relative risk =  $19.8\% / 23.3\% = 0.85$ .

**b.** Risk difference =  $19.8\% / 23.3\% = 3.5\%$

Number of patients who needed to be treated =  $1/0.035 = 29$  patients.

**c.** ICER (1000 patients) =  $\frac{(1000 \times 72.20) - (1000 \times 27.09)}{3.5\% \times 1000} = \frac{\$45\,110}{35}$

= \$1 288.86 per event avoided.

**d.** ICER (1000 patients)

$$= \frac{(1000 \times \$72.20) - (1000 \times (\$27.09 + 5 \times \$12.40))}{(1000 \times 23.3\%) - (1000 \times 19.8\%)} = \frac{-\$16\,890}{35}$$

Low-molecular-weight heparin is *dominant*. It is both cheaper and more effective than unfrac-

tionated heparin when monitoring costs are included.

*When a drug is dominant, it is not appropriate to calculate an ICER, as this can produce spurious results. Why do you think this is?*

#### 4.4. Celecoxib versus diclofenac

a. Relative risk =  $((38 + 11) / 212) / ((74 + 23) / 218) = 23\% / 44\% = 0.52$

b. Risk difference =  $23\% - 44\% = -21\%$

Number of patients who have to be treated to prevent a single event =  $1/0.21 = 5$  patients.

c. Dose of celecoxib = 400 mg/day. One pack contains sufficient drugs for 15 days of treatment. The duration of treatment is 24 weeks = 168 days. Therefore,  $168/15 = 11.2$  packs are required at a cost of  $11.2 \times \$50 = \$560$  per patient.

Dose of diclofenac = 100-150 mg/day. Assume a conservative dose of 100 mg/day.

One pack contains sufficient drugs for 25 days of treatment. The duration of treatment is 168 days. Therefore,  $168 / 25 = 6.72$  packs are required at a cost of  $6.72 \times \$11.60 = \$77.95$  per patient.

$$\text{ICER (1000 patients)} = \frac{(1000 \times \$560) - (1000 \times \$77.95)}{440 - 230} = \frac{\$482\,050}{210}$$

= \$2 295.48 per ulcer avoided.

#### d. Incremental cost per ulcer or erosion avoided

ICER (1000 patients)

$$= \frac{(1000 \times \$560 + 1000 \times 23\% \times 1\% \times \$1434) - (1000 \times \$77.95 + 1000 \times 44\% \times 1\% \times \$1434)}{(1000 \times 0.44) - (1000 \times 0.23)}$$

$$= \frac{\$479\,038.60}{210} = \$2281.14 \text{ per ulcer or erosion avoided.}$$

#### Incremental cost per hospitalization avoided

ICER (1000 patients)

$$= \frac{(1000 \times \$560 + 1000 \times 23\% \times 1\% \times \$1434) - (1000 \times \$77.95 + 1000 \times 44\% \times 1\% \times \$1434)}{(1000 \times 0.44 \times 0.01) - (1000 \times 0.23 \times 0.01)}$$

$$= \frac{\$479\,038.60}{2.1} = \$228\,113.20 \text{ per hospitalization avoided.}$$

#### Incremental cost per death avoided

ICER (1000 patients)

$$= \frac{(1000 \times \$560 + 1000 \times 23\% \times 1\% \times \$1434) - (1000 \times \$77.95 + 1000 \times 44\% \times 1\% \times \$1434)}{(1000 \times 0.44 \times 0.01 \times 0.1) - (1000 \times 0.23 \times 0.01 \times 0.1)}$$

$$= \frac{\$479\,038.60}{0.21} = \$2\,281\,136.20 \text{ per death avoided.}$$

4.5. *Oral montelukast versus an inhaled steroid*

- a/b.** There is no “right” answer to this question. What do you think?  
**c.** Beclometasone is both cheaper and more effective than montelukast. Therefore beclometasone is dominant.

**Chapter 5: Drug classification systems**

1. It is appropriate to assign an additional ATC code in N05A (Antipsychotics) for oral formulations of «Neurol», because the main indications for the parenteral and oral formulations differ. A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses (see *Guidelines for ATC classification and DDD assignment*. Oslo, Norway, WHO Collaborating Centre for Drug Statistics Methodology, version 2003.)
2. It is not appropriate to assign an additional ATC code in N04 (Anti-Parkinson drugs) for lisuride because the dosages overlap with those used in prolactin inhibition.

**Chapter 6: Drug utilization metrics and their applications**

1. Substance A: 250 mg  
Substance B: 300 mg
2. To make the sales figures comparable, it is important to recalculate the figures to reflect the same DDD version. The most recent DDD version should always be used (i.e. 0.8 mg for budesonide inhalation powder). Recalculation of the 1990 sales figure with the updated DDD gives 3.6 DDDs/1000 inhabitants/day.
3. Four-day courses, substance A: 1988: 0.43 million courses; 0.1 courses/inhabitant  
1996: 2.3 million courses; 0.57 courses/inhabitant  
  
Eight days courses, substance B: 1988: 2.7 million courses; 0.68 courses/inhabitant  
1996: 1.2 million courses; 0.31 courses/inhabitant



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## List of abbreviations

ACE inhibitors: angiotensin-converting enzyme inhibitors

AT: anatomical therapeutic (classification)

ATC: anatomical therapeutic chemical (classification)

CEA: cost-effectiveness analysis

CMA: cost-minimization analysis ICER: incremental cost-effectiveness ratio

CUA: cost-utility analysis DURG: WHO European Drug Utilization Research Group

DDD: defined daily dose

DU90%: drug utilization 90%

EPhMRA: European Pharmaceutical Market Research Organization

IMS: International Medical Statistics

MAO: monoamine oxidase

NSAIDs: nonsteroidal anti-inflammatory drugs

QUALY: quality-adjusted life-year

SSRIs: selective serotonin reuptake inhibitors

TCAs: Tricyclic antidepressants