Drug Utilization Studies
Methods and Uses

Edited by M.N.G. Dukes

WHO Regional Publications
European Series No. 45
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Drug utilization studies
Methods and uses
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Methods and uses

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Introduction

When introducing the concept of drug utilization studies to people who are not familiar with them, one is sometimes met with blank astonishment. Surely, the initial reaction goes, there is no shortage of statistics on the use of medicines already? Is it truly necessary to undertake so much work in order to obtain yet more?

The outsider’s first view of drug utilization research is understandable. There is something unexpected – indeed absurd – in the fact that in a world that uses so many medicines on so large a scale the pattern of their use is often so poorly known. Indeed there is no shortage of figures, but they are rarely the sort of figures that are needed to understand and interpret what is going on. Global statistics on the trade in drugs are rarely helpful; calculations based on expenditure can be highly misleading; and even individual physicians may have a mistaken idea as to their own prescribing pattern over a period of time, to say nothing of that of their colleagues. This is a field in which, for one reason or another, people working in the interests of public health have often found themselves labouring in the dark. Yet there are in fact some identifiable reasons why drug utilization has not always had the attention it deserves.

It is worth recalling that it was the pharmaceutical industry that first found itself in need of figures reflecting drug usage. Companies needed them to identify fields of opportunity for research and development, but also to monitor their own progress in a competitive market. Pioneering market research in this field was undertaken in the United States before 1939, paving the way for IMS (Intercontinental Marketing Statistics) which became a large and successful operation by documenting drug prescribing and sales in a wide range of countries, using continuous input from health professions and the market, and
making the results available in detail to industrial subscribers. Systems such as that operated by IMS could have served a broader interest as well, but as a rule the data they provided remained within the walls of industry. In part that was attributable to purely commercial factors; the data were costly to collect and analyse, and they could only be made available for a substantial fee. Yet even where public health authorities expressed willingness to pay the fee, they generally encountered a polite refusal; the polarization between the pharmaceutical industry and the public health authorities, which was widest after 1970, had perhaps created too much mistrust to expect complete openness on either side, and the fear was sometimes openly expressed that if governments had a complete insight into sales statistics they would take them as a basis for restrictive measures that would impede enterprise.

The fact remained, however, that as drug policy developed into a tangible entity in one country after another the need for such quantitative insight into the situation grew. It was needed to identify trends and set priorities not only in the interests of regulatory control but also as a basis for planning programmes of education and information; and where such initiatives were taken, reliable drug utilization data were again vital to determine how effective these measures had been.

The need for such information came to the fore just as an alternative way of finding it, other than through commercial channels, was gradually emerging, primarily as a consequence of the growth of national health insurance systems. The massive records kept by these systems had been designed initially for purposes of financing, administration and reimbursement, but their very size ensured they were among the first materials in the public sector to be computerized, and once computers replaced ledgers and adding machines more ambitious goals could be set. Statistics initially recorded in financial units could now be readily converted into terms more directly applicable to health studies. At the same time, the arrival of electronic data processing made accessible a mass of records long existing at other levels, particularly in the physician’s office and the retail pharmacy.

The beginnings of that development can be traced back to the early 1960s. Hans Friebel, a pioneer in the field, has recalled that it was in 1964, during a symposium on drug toxicology organized by WHO in Moscow, that serious consideration was first given to major public studies of drug utilization. Like many other developments at the time, this one had been sparked by the thalidomide disaster – if one had no
idea of the scale on which (and the manner in which) such dangerous products had been employed, how could one assess the frequency and location of risks? The Moscow meeting led directly to a joint study undertaken by two directors-general of public health – Dr P. Siderius in the Netherlands and Dr A. Engel in Sweden – who collected data not only from their own countries but from a range of others. Their findings were laid before a historic meeting at Oslo in 1969, and provided the basis for the formation of the WHO Drug Consumption Group, later to become the WHO Drug Utilization Research Group. It is a venture that has never looked back.

During the rather more than 20 years that have elapsed since then, the Group has remained very much the dynamo of drug utilization studies, and has done much to spread what was originally a northern European project to all parts of the world. A venture that was undoubtedly motivated at the start largely by economic considerations has become one very much serving the interests of efficient, effective and safe medicine. The Group – and the investigators and institutes associated with it – has developed and tested the instruments and methods essential if drug utilization studies are to be performed reliably and in a reasonably standardized fashion. Its work has moved progressively beyond methodology into interpretation and action; a first step might be to detect differences in the treatment of hypertension or diabetes between two countries or regions, but that led the Group’s eager scientists directly on to further questions, seeking both the causes of those differences, their consequences for public health, and ways in which one region might be induced to benefit from the experience of another.

That the present publication appears is in no small measure due to the initiative of the Catalonian Institute of Pharmacology, which in December 1986 convened the first meeting of authors and editors. The book is in part a record of what has been achieved, but it is primarily a guide to people who are ready to enter the field themselves or to extend their experience. They will certainly include both undergraduate and postgraduate students and researchers, but also many who approach the field from their work and experience in pharmaceutical administration or the pharmaceutical industry. Particularly for those concerned with the field of pharmaceuticals in central and eastern Europe, where the scene is undergoing such rapid change, it is essential to grasp the elements of drug utilization research. But even for those who have been engaged in the field for a longer period, a survey such
as this can point the way to work that must still be undertaken if the insight that is so necessary is to remain up to date and informative. Drug utilization research has in many countries come of age, and it is playing an impressive role in health policy, as it must.

What must not happen is to become so impressed by the scale and sophistication of what has been done that one hesitates to join the venture, fearful of the resources and specialization it will demand. The fact that one can do so much in this field with a mainframe computer and prescriptions by the million most definitely does not mean that nothing can be done with more modest means. I recall a drug administrator on a small oriental island who pieced together the facts he needed with the help of a friendly tax inspector dealing with imports. More than one general practitioner in a Spanish village has sat down with the local apothecary to monitor his own prescribing. And I remember the pharmacist in a tiny hospital, far away in the South American jungle, who studied the drug utilization habits of a handful of doctors using no more than a pocket calculator, an old typewriter and a deal of common sense, helping them to help themselves to better prescribing. Common sense, patience and enthusiasm are the only truly indispensable elements in drug utilization studies; they underlie all the experience accumulated in this book.
General background

J.R. Laporte, I. Baksaas & P.K.M. Lunde

The Historical Prologue

Drug therapy as it exists today must be seen largely as an ultimate consequence of the developments in chemistry, physiology and basic pharmacology that took place in the nineteenth century. At the beginning of that century, most medicines in use were remedies of vegetable origin, whose chemical structure was unknown. As the century advanced, important progress was made in both chemical and physiological sciences, though only very few new drugs were introduced into therapeutics. Mann (1) quotes a list of the “best things” in the first British pharmacopoeia (1864) for the physician of the day: they comprised digitalis, opium, atropine, morphine, quinine, ether, chloroform, ferrous sulphate, iodine, sodium bicarbonate, and the sources of some of the vitamins, none of which had yet been described. From Table 1, which lists the dates of the discovery and first therapeutic use of some drugs, one can see how, in the course of nearly 200 years, the development of novel agents has progressively accelerated to reach the situation with which we are familiar today.

The process of change has, however, involved more than the spectrum of remedies available; the ways in which they are developed, presented and protected by law have also evolved, even within the lifetime of physicians still in practice. During the 1930s and even the 1940s, pharmaceutical products accounted for a very low proportion (often less than 25%) of all remedies sold in pharmacies, whereas today they account for over 80–90%. Within a decade of the end of the Second World War, the “drug explosion” was well under way. Fig. 1, taken from Reekie & Weber (2), clearly illustrates that explosion as reflected in the rapid increase in the number of pharmaceutical patents issued. Finally, and in parallel with these other developments, the scientific approach began to
Table 1. Some landmarks in the development of modern drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Landmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1803</td>
<td>Serturner reports isolation of morphine</td>
</tr>
<tr>
<td>1846</td>
<td>Morton demonstrates the effects of ether in anaesthesia</td>
</tr>
<tr>
<td>1847</td>
<td>Sir James Young Simpson reports the first use of chloroform in anaesthesia</td>
</tr>
<tr>
<td>1867</td>
<td>Lister introduces antiseptic surgery</td>
</tr>
<tr>
<td>1875</td>
<td>Buss uses sodium salicylate as an antipyretic and for rheumatic fever for the first time</td>
</tr>
<tr>
<td>1877</td>
<td>Laqueur reports the therapeutic use of physostigmine in the treatment of glaucoma; its chemical structure, however, is only elucidated in 1923</td>
</tr>
<tr>
<td>1882</td>
<td>Koch reports the discovery of the tubercle bacillus</td>
</tr>
<tr>
<td>1883</td>
<td>First use of paracetamol by von Mering</td>
</tr>
<tr>
<td>1899</td>
<td>Dreser introduces acetylsalicylic acid</td>
</tr>
<tr>
<td>1903</td>
<td>Introduction of barbital</td>
</tr>
<tr>
<td>1911</td>
<td>Ehrlich introduces the arsenical compound 606 (Salvarsan) for the treatment of syphilis</td>
</tr>
<tr>
<td>1912</td>
<td>Introduction of phenobarbital</td>
</tr>
<tr>
<td>1922</td>
<td>Banting and Best discover insulin and use it for the first time</td>
</tr>
<tr>
<td>1935</td>
<td>Domagk reports the use of prontosil red (sulfamidochrysoidine)</td>
</tr>
<tr>
<td>1936</td>
<td>Fourneau and colleagues report on the effect of sulfanilamide in curing experimental infections</td>
</tr>
<tr>
<td>1938</td>
<td>Merritt and Putnam discover the anticonvulsant properties of phenytoin and report its use for the symptomatic treatment of epilepsy</td>
</tr>
<tr>
<td>1939</td>
<td>Eisleb and Schaumann introduce the use of pethidine</td>
</tr>
<tr>
<td>1940</td>
<td>Chain and Florey report the isolation of penicillin</td>
</tr>
<tr>
<td>1941</td>
<td>First clinical use of penicillin</td>
</tr>
<tr>
<td>1943</td>
<td>Thousands of 4-aminoquinoline derivatives are synthesized and tested for activity, in connection with an extensive cooperative programme of antimalarial research in the United States during the Second World War; chloroquine is released for field trial; when hostilities cease, it is discovered that the drug had been studied under the name of Resochin by German workers in 1934</td>
</tr>
<tr>
<td>Year</td>
<td>Landmark</td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>1944</td>
<td>Schatz, Bugie and Waksman announce the discovery of streptomycin; from 1947 to 1952 streptomycin is the only effective antituberculosis drug available</td>
</tr>
<tr>
<td>1948</td>
<td>Introduction of chlortetracycline, the first tetracycline, soon followed by oxytetracycline (1950) and tetracycline (1952)</td>
</tr>
<tr>
<td></td>
<td>Introduction of chloramphenicol</td>
</tr>
<tr>
<td>1951</td>
<td>Introduction of isoniazid for the treatment of tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Introduction of procainamide as an antiarrhythmic</td>
</tr>
<tr>
<td>1952</td>
<td>McGuire and colleagues discover erythromycin</td>
</tr>
<tr>
<td></td>
<td>Laborit demonstrates the effects of chlorpromazine and Delay and Deniker are the first to use it in psychiatric patients</td>
</tr>
<tr>
<td>1954</td>
<td>Demonstration of the clinical effects of sulfonylureas in diabetes</td>
</tr>
<tr>
<td></td>
<td>First report on the antifungal properties of nystatin</td>
</tr>
<tr>
<td></td>
<td>First report on the use of meprobamate as a sedative</td>
</tr>
<tr>
<td>1955</td>
<td>Extensive field studies with hormonal oral contraception in San Juan de Puerto Rico</td>
</tr>
<tr>
<td>1957</td>
<td>Iproniazid is introduced for the treatment of depression</td>
</tr>
<tr>
<td></td>
<td>Sternbach's group at the Roche Laboratoires develops chlordiazepoxide</td>
</tr>
<tr>
<td>1958</td>
<td>Kuhn recognizes the antidepressant effect of imipramine</td>
</tr>
<tr>
<td></td>
<td>Janssen discovers the antipsychotic properties of haloperidol</td>
</tr>
<tr>
<td>1960</td>
<td>Durel and colleagues introduce metronidazole as a trichomonacidal</td>
</tr>
<tr>
<td>1964</td>
<td>Sir James W. Black reports the discovery and development of beta-blocking agents</td>
</tr>
<tr>
<td>1972</td>
<td>Sir James W. Black reports the discovery and development of antihistamine H2 drugs</td>
</tr>
</tbody>
</table>

Source: Most of the dates included in this table have been taken from Goodman, L.S. & Gilman, A. The pharmacological basis of therapeutics, 7th Edition. New York, Macmillan, 1985. Others have been taken from standard textbooks of pharmacology.
evolve in pharmacology and medicine, and was destined to develop to the point where the scientific assessment of drugs would be both feasible and generally accepted. Fig. 2 shows the history of the development of a new drug. Even if much information has been systematically obtained during the preclinical stage of drug development and during the premarketing clinical studies, knowledge of the drug’s effects at the time of its release is inevitably incomplete and may prove to have been very limited.

Fig. 1. Rise in the number of chemicopharmaceutical patents issued from 1910 to 1966 (in five-yearly periods)

![Graph showing the rise in the number of chemicopharmaceutical patents from 1910 to 1966.]

Note. The 1910 observation is based on all earlier data.

Source: Reekie & Weber (2).

The rapid introduction of thousands of different products for therapeutic use coincided with an increasing demand for health services. The latter was the result of developments in the economy and in living standards, and of the creation of social security systems, national health services and schemes for reimbursement of the costs of drugs; the expansion of the therapeutic arsenal, however, also very clearly reflected the pressures exerted by drug manufacturers, ever seeking to ensure a constant expansion of their market.
Fig. 2. The history of the development of a new drug

**Discovery**
Based mostly on systematic research, including screening of natural products and/or chemical synthesis

**Physicochemical characterization**

**Preclinical pharmacological studies**
- pharmacodynamics
- pharmacokinetics

**Preclinical toxicological studies**
- acute toxicity
- subchronic toxicity
- chronic toxicity
- mutagenicity, teratogenicity, carcinogenicity

**Clinical studies**
Phase I: early studies in volunteers
Phase II: early measurement of activity and dose-finding studies
Phase III: therapeutic trials to establish efficacy (randomized controlled clinical trials)

?
The increase in drug consumption has been far from uniform around the world. In 1976, for example, the developing countries, with 63% of the world's population, accounted for only 22% of the world's pharmaceutical market by value (2). By 1985, the global drug bill was estimated at US $100 billion annually, of which developing countries, now with 75% of the world's population, accounted for only US $15–20 billion (3). Any fuller analysis of the situation must, however, also reflect the fact that in many non-industrialized countries large segments of the population, living in rural areas, have little or no access to medical care and are commonly unable to pay for such care as may become available. These facts have repercussions in turn for drug research and development, which tend to be largely directed towards the markets that can carry their costs and may take little account of real health needs elsewhere.

The increase in the use of pharmaceuticals, backed by aggressive promotion in a manner unknown for any other form of health care, has had an obvious cultural impact: it has increased dependence on allopathy, and therefore on doctors and pharmacists as social groups, and it has tended to supplant other traditions of care and healing (3).

**Drug Evaluation in the Community**

Any attempt to quantify the effects of modern drug therapy must be balanced if it is to be meaningful. The process of drug evaluation is usually seen today as a composite undertaking that includes three complementary steps:

- the assessment of the "benefit" side of the molecule or product, i.e. the qualitative and quantitative evaluation of its therapeutic efficacy;

- the study of the "risk" side of the drug, both in controlled trials and under normal conditions of care; and

- the evaluation of the impact of the drug treatment(s) on the natural history of disease in society.

Even the first two elements in this process have only gradually received the attention they deserve from researchers and legislators, and sometimes only through a hesitant process of trial and error. The third element – the evaluation of social impact – remains even today and in
industrialized countries highly problematic. For example, the beneficial effects attributable to drugs may be difficult to distinguish from those caused by improvements in nutrition, housing or hygiene, the supply of clean water, better food storage, antenatal and infant welfare care, greater economic security, improved education, changing patterns in the natural history of disease, shifts in social habits such as smoking, occupational exposure, and a host of other factors.

Evaluation of benefit
The beneficial effects of drugs were most acutely realized during the 1940s and 1950s, when the introduction of antibiotics gave physicians a means of saving life in conditions that up to that time would have been commonly or inevitably fatal. The results obtained with this class of drug (as also with the new poliomyelitis vaccines) were so dramatic and readily discernible, however, that they provided little in the way of an impulse to develop sound methods for evaluating drug efficacy. Only with the emergence, during the years that followed, of clinical pharmacology and epidemiology did the science of conducting clinical trials develop, a methodology that was to be greatly refined during the 1960s and 1970s. The efficacy of new drugs came to be routinely tested in randomized controlled studies; at the same time, the new methods threw doubt on the hitherto unquestioned efficacy of many drugs dating from an earlier period, some of which now had to be characterized as useless; in particular, the critical study of fixed-dose combinations of two or more drugs showed that a large proportion of such mixtures were irrational or even dangerous. The new science also provided other shocks and surprises; sometimes even drugs that had come relatively recently into routine use in the long-term treatment of certain diseases (such as oral hypoglycaemic agents used in type II diabetes (4)) failed to show a beneficial effect in randomized controlled trials.

One must add, however, that society has not always been quick to benefit from such new findings and insights. Some irrational fixed combinations continue to rank among the top-selling drugs on certain national markets; drug statistics have shown that in a number of countries many of the drugs still most widely consumed are devoid of proven efficacy (5,6). Even for drugs marketed more recently, one sometimes finds profound weaknesses in the clinical trials that were supposed to demonstrate their value, yet it can prove extraordinarily difficult to set aside a therapy originally accepted on the basis of what originally appeared to be valid data (7).
As society progressively became aware of the need for rigorous methodology in clinical trials, so legislators moved to introduce reasonable proof of efficacy as a basic element in drug regulation. This too was a slow process. The principle did not become at all generally accepted until the growth of clinical pharmacology during the 1960s and 1970s demonstrated how serious and how common the shortcomings were, and provided at the same time ever better instruments for assessing the evidence as to whether a drug was truly effective in humans or not (8).

**Evaluation of risk**
The possibility that drug use could result in adverse reactions came to the fore rather earlier than did concern about inefficacy. For example, the first suspicion that drugs might be involved in causing aplastic anaemia was aroused by Labbé & Langlois in 1919 (9), 31 years after the first description of the disease (10). In 1934, the role of a drug in the etiology of agranulocytosis was suggested for the first time (11). The epidemic of more than 100 deaths that resulted from the marketing of a solution of sulfanilamide in diethylene glycol during the 1930s in the United States (12) resulted in an amendment of federal legislation to provide better guarantees of safety.

It was in November 1961 that Lenz, a German paediatrician, declared that he had traced a current outbreak of an extremely rare gross malformation, phocomelia, to the use in pregnancy of the new hypnotic drug thalidomide (13). In December 1961, the first report of the association to appear in a widely circulated medical journal was published, indicating that thalidomide might be a human teratogen (14). The drug was withdrawn from the market early in 1962. The total number of cases may have been in the neighbourhood of 4400, of which 498 are known to have proved fatal at the time of birth or later (15). A review of the experimental work carried out with thalidomide before marketing revealed that inappropriate toxicological data had been published and animal findings misinterpreted (16), but there can be no doubt that, in this instance, the human tragedy itself proved the case and that the correlation between experimental and human data, which was not a close one, was misinterpreted as well.

Thalidomide was by no means destined to be the last or greatest of the drug disasters. During the 1960s a synthetic estrogen, diethylstilbestrol (DES), gained popularity among obstetricians, particularly in the United States, as a supposed means of preventing miscarriages (see Fig. 3). The evidence supporting the use of DES in this indication was very weak, and
This advertisement for diethylstilbestrol appeared in a major obstetrical journal in 1957, some 14 years before the drug was exposed as a major teratogen.
was not based on properly conceived clinical trials (17). A double-blind, placebo controlled study with over 1600 women (18) concluded in 1953 that DES “did not reduce the incidence of abortion, prematurity or postmaturity. Premature babies were no more mature for their gestational age”. But such a report was insufficient to break what had become an established prescribing habit. By 1971, DES had been taken by an estimated three million women in the United States alone (17), although it is believed that by far the highest rate of use in any population was that in the Netherlands. That same year, a study was published showing that taking DES during pregnancy was associated with a risk of a rare form of vaginal cancer known as clear cell adenocarcinoma, developing in the offspring when they became adult (19). By the end of 1971, the Food and Drug Administration (FDA) had declared that DES was contraindicated in pregnancy and other agencies followed its lead. Nevertheless the use of DES during pregnancy was not immediately abandoned; its use ceased only in 1973 in the Netherlands and as late as 1978 in Spain. With the benefit of hindsight one must unhappily conclude that the risks of DES identified in 1971 were not the only ones; more recent studies have shown that in utero exposure to DES increases the risk of genital structural anomalies and malformations, infertility, ectopic pregnancy, miscarriages, preterm labour and premature births among the daughters, as well as the incidence of other urogenital malformations among the sons (20).

Drug Surveillance Schemes for Adverse Drug Reactions

Schemes to monitor adverse reactions to drugs were developed during the 1960s in some countries, and the WHO international programme for drug monitoring was set up in 1964 (21). Some 30 nations now participate in this programme, though most of these are developed western nations. Drug surveillance schemes have helped to identify risks and to identify patient groups at special risk. They have also played an educational role, having a clear influence on prescribers, health authorities, the pharmaceutical industry and the public, although all too often the data emerging from these schemes have been unquantifiable, particularly because of a lack of reliable figures on the extent of use of the drugs concerned.

Drug Statistics

Although the overall effect of medicines on the health of the community has not in most cases been adequately quantified, the level of drug use has
risen considerably, particularly in certain countries. In 1982, 11.3 drugs were prescribed per head in Italy, 11.2 in the Federal Republic of Germany (prior to the accession of the former German Democratic Republic), 10 in France and 9.6 in Spain, as opposed to only 6.5 in the United Kingdom (22). To obtain the complete picture, data on non-prescription drugs must be added, sometimes accounting for something like a fifth of the total.

What proportion of this turnover represents appropriate use remains a question that one cannot answer completely; certainly, research in clinical pharmacology has repeatedly shown that drugs are often not used to their full potential, either in terms of efficacy or of safety (23). Even where a drug or other therapeutic measure has been shown to be effective in a randomized clinical trial, it may still prove useless if prescribed or employed in an inappropriate manner — for example, if given for the wrong purposes, in an incorrect dosage, or for the wrong period of time (24). Many studies suggest that much prescribing may indeed be unnecessary, inappropriate, or irrational (25, 26). In addition, both physicians and patients are well aware that there is a disparity between the prescription and the taking of medicines (27). Finally, optimistic expectations based on the results of clinical trials may for various reasons fail to be fulfilled when a drug comes into use in the field (see Chapter 2).

The thalidomide disaster, which did so much much to draw attention to the problem of drug-induced injury, resulted at the same time in a new and critical view of the established prescribing habits of physicians. In 1969, Stolley & Lasagna (25) noted that:

the endpoint of the patient–physician encounter is the writing of a prescription in an estimated two-thirds of all patient visits; and yet relatively little is known of the prescribing patterns of physicians. The recent proliferation of new drugs, their widespread use and powerful actions, the increasing recognition of immediate and delayed adverse effects and the increasing concern about the cost of drugs have stimulated a new interest in the manner in which physicians prescribe drugs.

Yet another factor that focused attention on these issues was the economic problem of the sheer cost of drugs to the community, which had continued to rise even as the state of national economies passed its peak and sometimes went into sharp decline. The proportion of health expenditure devoted to drugs is high but very variable; in Europe it varies from 7–9% in the Nordic countries to 20% in Spain, 21% in Italy, and 23% in Switzerland. Even allowing for some artefacts in the comparison, such variations certainly reflect differing political options in the field of health in each country.
The mounting concern of national health systems about the level of drug expenditure was a major incentive in the development of better statistics on drug usage, and particularly of figures independent of those produced by drug companies or for marketing purposes. Because some of the earliest work was inspired by these economic concerns, the statistics that emerged were oriented towards costs and prices rather than issues of health or matters of epidemiology. They nevertheless opened the eyes of many people to the possibilities for further study and the value that such figures might have in the study of trends and quality in therapeutic care.

The initial studies were therefore soon complemented by investigations into the prescribing habits of physicians. In the early 1950s, Martin analysed a large number of prescriptions issued by general practitioners under the British National Health Service, finding striking regional differences in prescribing (28). Rather later, investigators sought to relate usage to real need; in a paper that is a landmark in the history of drug utilization studies, Cochrane & Moore showed in 1971 that in the United Kingdom, just as had been demonstrated in Denmark, the total consumption of vitamin B_{12} was 3–20 times higher than might reasonably be considered necessary (29).

Such concerns about the safety, efficacy, costs and appropriateness of care pointed to the need for a comprehensive analysis of the factors determining drug consumption. The first international survey with that aim was carried out by Engel & Siderius (30). They showed wide international differences in drug registration traditions and in patterns of use, but they could not explain these differences. At a now historic symposium convened by the WHO Regional Office for Europe in Oslo in November 1969, the methodology for future international studies was discussed (31) and WHO’s Drug Utilization Research Group (DURG) was born. A direct consequence was to be the development and acceptance, both within the Nordic countries and within the DURG as a whole, of a common drug classification and a common unit for measuring drug consumption, both of which rendered valid international comparisons possible (see Chapter 4). The development and maintenance of the defined daily dose (DDD) unit has allowed it to become one of the classic pillars of drug utilization studies (32–34).

From an early phase, however, it was clear that the drug utilization venture could and must do a great deal more than address the methodological issues. Its greater potential and its more ambitious goals were reflected in the WHO definition of drug utilization (35): “the marketing,
Table 2. Aspects and consequences of drug utilization to be explored

<table>
<thead>
<tr>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits: efficacy in preventing, relieving and curing diseases or their symptoms and complications</td>
</tr>
<tr>
<td>Risks: short-term and long-term adverse effects, special risk factors associated with genetics, disease and environment, nutrition, age, sex, pregnancy, lactation, etc.</td>
</tr>
<tr>
<td>Benefit/risk ratio: the extent to which inappropriate prescribing or use may reduce benefits and increase risks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitudes to drugs and health and their basis; current trends in the “drug culture” versus persistent or resurgent use of traditional medicines</td>
</tr>
<tr>
<td>Drug abuse and dependence and their causes and trends</td>
</tr>
<tr>
<td>Improper use of drugs (non-compliance, use of drugs for purposes for which they were not prescribed or recommended); incidence and explanation</td>
</tr>
<tr>
<td>Discrimination and social injustice (e.g. unavailability of important drugs to those who need them)</td>
</tr>
<tr>
<td>Effect of information and regulatory measures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Economic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug and product prices and costs; imports versus local production; costs of new drugs versus old drugs and of specialities versus generic products; costs of drug versus non-drug treatment</td>
</tr>
<tr>
<td>Drug cost/effectiveness/safety ratios for all the comparisons listed above</td>
</tr>
<tr>
<td>Current and future allocation of national resources (money, personnel, facilities) to the drug and health budget</td>
</tr>
</tbody>
</table>

Source: Baksaas & Lunde (36).
distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”.

Drug utilization studies have indeed developed in this direction and continue to develop further; some current and future matters for study are suggested in Table 2. Work of this type provides a powerful and exploratory tool to document the role of drugs in society (36) and thereby to create a sound sociomedical and health economics basis for regulatory and other policy decisions. The value of up-to-date and freely available drug surveys of statistical validity as a common basis for discussion, debate and policy-making has been strikingly demonstrated in the Nordic countries (37, 38). Despite the relatively limited effort involved, drug statistics have become an important means of profiling the career of drugs over time, of identifying potential problems for further research, and of measuring the effects of regulatory and informational initiatives (39). Improved communication on drug utilization matters between the various categories of users within the health service and the administration is another positive consequence (36).

Factors Influencing Drug Consumption

One might expect that drugs are prescribed and taken in order to prevent, alleviate or cure illness, and essentially that is true. The fact, however, that patterns of usage and of illness do not run parallel points to the existence of factors other than basic need that influence drug consumption, factors that may be unrelated to the actual properties of medicines being taken. These factors have been called the “non-pharmacological basis of therapeutics” (40), and they deserve particular attention at this point in the story.

At the most basic level, the patterns of drug consumption in a country will reflect to a greater or lesser extent that country’s scientific and technological traditions as well as its sociodemographic state and culture. More specific is the influence of traditional medical practices and patient expectations, the structure and organization of the health services, the economic state of these services – including the pricing of medicines and the nature of social security and reimbursement systems – and the effects of various forms of regulation or coercion, ranging from national approval procedures to the role played by local drug committees. At the same time, drug consumption will be swayed by the promotional activities of the drug industry, the structure and the interplay of national and multinational firms, professional and public pressures, changing
preferences and attitudes, the training of prescribers in drug use, and efforts from truly or allegedly independent sources to provide information and advice both to prescribers and to the public.

Because all these influences exist, the results of drug utilization studies will sometimes cast some light on the health system itself and the influences operating on it. If one can gain a broad understanding of the way in which drugs are developed, registered, promoted and used, this will provide a series of excellent markers for understanding the “metabolism” of the health system itself. The second generation of drug utilization studies, in which the DDD methodology came to be used, has for that reason sometimes been characterized as the investigation of drug pharmacokinetics in the community (41). A third generation of drug utilization studies, which are now coming into being, will necessarily focus to an increasing extent on the ultimate question: what are the effects of drug use on the health of the community? This could well be termed the community pharmacodynamics of drug use. New methods will need to be developed for that purpose, and for the no doubt even more ambitious studies that will carry us into the twenty-first century.

References


From clinical trials
to drug utilization studies

G. Tognoni & J.R. Laporte

The background to this chapter and the challenge it is concerned with may be found in an editorial (1) some years ago hailing a major event in the practice of medicine: “the end of clinical freedom”. The provocative title was an appropriate summary not only of the contents of the editorial itself but of more than 30 years of often controversial developments, all related to the emergence of the principle that clinical practice, both diagnostic and therapeutic, must be based only on interventions that have been properly tested with controlled methods, in particular randomized controlled clinical trials.

In itself, that principle hardly seems provocative; it merely echoes the message of an increasing number of publications and consensus recommendations, including a few books that stand as milestones in the development of clinical therapeutics this century. All these call for a systematic and ethical approach to the practice of medicine on the part both of physicians and of the public; all of them point to the absolute need for clinical research based on the randomized trial approach (2–5). The provocative side of the title surfaces, however, when one realizes that much of what doctors do for their patients still fails to meet these essential requisites. The “end of clinical freedom” is simply the end of a long era during which the widespread use of familiar yet unproven methods was regarded as normal and natural. It is therefore a welcome step forward, but it is a step that must indeed be taken and not merely discussed. Is it realistic to expect that the slow movement of medicine towards more generalized adherence to scientific standards will accelerate to meet the challenge and the duty suggested by that editorial? Can controlled methodologies and protocols be applied to the entirety of diagnostic and therapeutic practice? How will one determine where exceptions to the rule can be made, so as to
maintain a proper degree of clinical freedom without providing an excuse for empiricism or sloppy practice? Such questions are only a sample of those that must arise about the standards day-to-day clinical practice should seek to meet. What we shall consider here is the potential offered by drug utilization studies to monitor and perhaps facilitate progress towards such ideals.

There is simply no doubt that properly conducted randomized clinical trials provide a reliable and widely accepted method for demonstrating whether or not a given intervention is able to produce the effect claimed for it. Equally beyond doubt is the fact that the principle is widely ignored. The degree of variation in drug use from country to country and within individual countries is particularly striking; sometimes therapeutic behaviour seems to be largely a matter of opinion. No one can say what effects such an approach has on the health of individual patients or of entire populations, exposed as they appear to be to a curious and variable blend of empiricism and tested knowledge ((6–11); see also chapters 1 and 4).

This is not the place for an exhaustive analysis of the phenomenon, let alone any comprehensive plan for dealing with it. What we can attempt to do, however, is to propose a reasonable and practicable sequence of steps to bridge the gap between the methods and experience acquired in controlled studies of drug efficacy and the knowledge and techniques built up in the last two decades through the study of drug utilization. Up to now, experts in these two fields have developed respect for one another's work without developing any close links. The separate paths followed by the two disciplines are sketched in Fig. 1, which suggests some reasons for their relative isolation from one another. One must also realize, however, that in neither of these fields is one always sure of the actual relevance of the work to practical medicine, or of its current influence in the field; clearly, for example, it would often be wrong to apply to an entire population the results of studies in a selected subgroup (12). The sort of questions listed in the final boxes on each track in Fig. 1 are all too commonly unanswerable.

Randomized Controlled Clinical Trials and the State of the Drug Market

Despite the claims advanced in most drug-producing countries that laws and regulations set adequate standards of drug evaluation to protect the public interest, it is well known from the literature and
Fig. 1. Parallels and overlaps between randomized clinical trials and drug utilization studies

**The questions and the paths of**

**randomized clinical trials**

(for the controlled evaluation of drugs)

- Does drug A have a pharmacological effect?
  - How does this effect interplay with the underlying pathophysiology of the disease?
- Is drug A $\leq$ drug B (or placebo)?
  - What is the therapeutic effect needed if it is to be considered:
    - clinically relevant?
    - statistically reliable?
- Are the risks associated with the new treatment compatible with an overall positive judgement of it?
- Does the new treatment add to, substitute for or reproduce existing therapeutic strategies?
  - Do results confirm or falsify the hypotheses on which the controlled experiment was based?
- How will the benefit/risk ratio shown in experimental conditions apply to the whole population?
  - What will the impact of the new treatment be on the disease with respect to:
    - its course and outcome in the community?
    - its understanding by physicians?

**drug utilization studies**

- How are drugs used, quantitatively, qualitatively, in different societies?
- What are the factors that determine similarities or differences?
- What is the fraction of patients exposed to treatment(s):
  - according to accepted standards?
  - according to casual criteria?
  - according to schedules that positively differ from those tested in randomized clinical trials?
- Do the patterns of drug use (extension, quality) have any connection with the occurrence (overall or drug-class specific) prevalence of side effects?
- What is the impact of different conditions of drug use such as over-, under-, wrong prescribing, on the population, with respect to:
  - care and health?
  - adverse reactions?

**Epidemiology and natural history of problems and diseases**
from experience that a large proportion of the drugs on sale today have undergone no reliable and systematic evaluation for efficacy or safety. The problem has various facets.

1. Many drugs that are still widely prescribed were launched before controlled evaluation was required for market approval; the process of re-evaluation, where applicable, tends to be slow, and may itself be determined more by empiricism than by a methodological scientific approach, assessors readily relying on such factors as “long experience in the field” and being prone to give popular drugs the benefit of the doubt (13, 14).

2. The marketing of drugs (and promotion of indications) using assertions unsupported by scientific evidence of efficacy remains widespread. The many critical and independent drug bulletins (including those circulating in France, Germany, Italy and Spain) continually draw attention to this phenomenon (15–19).

3. Many existing fixed-combination products (which in the countries cited above may account for up to 40% of the market) have never been adequately tested against their individual components or against a standard reference drug. Such tests may be laborious—Table 1 shows how many groups of patients may be needed to prove the superiority of a fixed-dose combination—but they are necessary if one is to separate the wheat from the chaff.

4. “Me-too” drugs (whose active principles are closely similar to compounds developed earlier) rarely undergo exhaustive study; once their activity has been demonstrated, it is all too readily assumed that they will be as usable in a range of indications as the compounds that inspired them; plainly this may not be the case (20).

5. Only a few of the so-called randomized clinical trials of efficacy published every year are in fact based on reliable methods (21–23). In many trials with non-steroidal anti-inflammatory and analgesic drugs, for example, the groups used are too small; of 80 comparative trials surveyed by Bland et al., 6 were found to have involved fewer than 11 patients, 16 between 11 and 20 patients, and 44 fewer than 31 patients; only 8 trials included more than 100 patients (24). This example is by no means unique. A detailed survey of all the
Table I. Number of groups of patients needed in a clinical trial to demonstrate the efficacy of a fixed-dose combination of two or more drugs

<table>
<thead>
<tr>
<th>Number of drugs to be tested</th>
<th>Number of groups of patients at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>one-dose level</td>
</tr>
<tr>
<td>One (A)</td>
<td>3(^b)</td>
</tr>
<tr>
<td>Two (A,B)</td>
<td>4(^c)</td>
</tr>
<tr>
<td>Three (A,B,C)</td>
<td>8</td>
</tr>
<tr>
<td>Four (A,B,C,D)</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\) Two groups, one treated with A and another with the reference treatment.  
\(^b\) Three groups, one treated with A at a low dose, another with A at a high dose and a third with the reference treatment.  
\(^c\) Four groups, one treated with A, another with A + B and a fourth with the reference treatment.  
\(^d\) And so forth, the reader may do the exercise for each situation in this table.

randomized clinical trials of psychotropic drugs published from 1981 to 1987 in the world’s main psychiatric and general medical journals (comprising a total of more than 200 papers) showed that many of them were based on designs adequate only for small pilot studies (25). Similar observations may well apply to work in other major therapeutic fields.

For all these reasons and others, then, proof of efficacy is often inadequate even today. Proof of safety is likely to be even more deficient in view of the extraordinarily stringent methodological conditions that must be met if evidence of risk is not to be missed (26–29).

Relevance of Randomized Clinical Trials to Prescribing Practice

Before the knowledge about the efficacy of a drug that emerges from randomized clinical trials can be turned into an actual benefit for a target population, a somewhat indistinct, but nevertheless very formidable barrier must be passed, namely the ambiguity of the prescribing doctor’s situation and approach (30–32).
Sometimes the physician's reaction is barely logical. The belief that "I must do what is good for my patient" may prevail, even in the face of objective evidence from other parties that what is being done is not so good after all. On occasion, a resistance to innovation is discernible and at other times a willingness to accept whatever is new even if unproven. The physician may also be subject to positive or negative pressures from peers or patients and will most certainly be exposed to commercial persuasion. Such influences compound the genuine difficulty many physicians have in determining the real therapeutic significance for the individual patient of trial results expressed in degrees of probability. For all these reasons and others, the knowledge acquired in controlled clinical trials may have much less of an effect on practice in the field than one might in theory expect.

We must stress, however, that randomized trials do not always produce results that are suitable for direct transfer to real populations of patients. The setting may be different (Table 2), the process of progressive selection in trial group and cohort as an investigation proceeds may result in a comparison of less than universal validity (Fig. 2 and 3), and the statistical significance of the results may be marginal. The question of how representative trial subjects are of the treated population at large is particularly important for illnesses with multiple alternative causes or prognoses, and those where the reaction to treatment differs widely between patients. These conditions typically pertain to most diseases where a sizeable proportion of patients are unresponsive to treatment, or where the drug in question is generally only one component of an overall treatment strategy.

While it may be relatively simple to detect and correct basic faults of method in a trial protocol, ensuring representativeness is a major methodological and cultural challenge. Fortunately, some very large-scale trials recently conducted have used settings and criteria that closely mimic routine practice; they show that the challenge can be successfully met (36–39). Table 3, based on one of these studies, outlines the essential characteristics of the approach. The term "population trials" has sometimes been used to describe this method, which was originally conceived because of the need to recruit large enough cohorts to allow a reliable estimate of even a small but clinically relevant effect (Table 4). The focus is more on the populations with the disease and less on the drug treatment which, as far as possible, is tested in the natural environment in which it would be prescribed, to determine whether in that situation it can modify the natural course of
Table 2. The settings of randomized clinical trials and of routine practice

<table>
<thead>
<tr>
<th>Features of setting</th>
<th>Randomized clinical trial</th>
<th>Routine practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selection</td>
<td>Accurate diagnosis</td>
<td>Diagnosis not always reliable</td>
</tr>
<tr>
<td></td>
<td>Groups at special risk</td>
<td>Borderline and complicated</td>
</tr>
<tr>
<td></td>
<td>or with accompanying</td>
<td>patients may be frequent</td>
</tr>
<tr>
<td></td>
<td>diseases excluded</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>&lt; 100-1000</td>
<td>&gt; 10000 ?</td>
</tr>
<tr>
<td>Control</td>
<td>Often double-blind</td>
<td>Open, reflects expectations</td>
</tr>
<tr>
<td></td>
<td>conditions</td>
<td>and prejudices of prescribers</td>
</tr>
<tr>
<td></td>
<td>Well defined criteria for</td>
<td>Data collected without</td>
</tr>
<tr>
<td></td>
<td>complete data collection</td>
<td>formal rules</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses</td>
<td>Generally fixed</td>
<td>May be higher or lower</td>
</tr>
<tr>
<td>Duration</td>
<td>Usually shorter than the</td>
<td>Depending on many factors,</td>
</tr>
<tr>
<td></td>
<td>expected natural history</td>
<td>often shorter or longer than</td>
</tr>
<tr>
<td></td>
<td>of the problem (except</td>
<td>the trial</td>
</tr>
<tr>
<td></td>
<td>for acute symptoms or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>treatment)</td>
<td></td>
</tr>
<tr>
<td>Other drugs</td>
<td>Excluded as far as possible</td>
<td>Often present</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Based on defined</td>
<td>Based on a &quot;clinical</td>
</tr>
<tr>
<td></td>
<td>endpoints</td>
<td>judgement&quot;, or possibly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>secondary criteria</td>
</tr>
</tbody>
</table>

The results, whether clear-cut (37, 38) or borderline (39, 40), provide an estimate not only of the effect of the drug, but also of the impact of the treatment on the epidemiology of the disease, when administered in clinical practice and free of the constraints that are inevitable in the setting of a trial.

The technique and practice of trial overviews (or meta-analyses) are developing concurrently. In a sense, they make it possible to estimate the extent to which the variations in a treatment’s effect, when using different schedules in not strictly identical populations, represent
the range of response likely to be encountered in routine conditions of care ((41–47); see Fig. 4 and 5 for examples).

Once the exclusive realm of drug experts, randomized trials have come to interest and involve the very clinicians who will be using the drug in patients similar to those randomized into the trial. The boundaries between clinical experimentation and epidemiology thus become less absolute. Drug questions may have lost some of their pharmacological specificity and separateness, but they have acquired a broader role: they are one of the deliberate interventions that may influence the course of a disease in a population. From such an angle the problem of the non-responder can be better examined than before; the biochemical or genetic factors that determine the fate of a drug in the organism and explain such differences in pharmacological response can now be viewed in the broad light of the epidemiological heterogeneity of the disease. One will also be able to define the drug’s potential therapeutic usefulness and the criteria for evaluating overall response, in terms closer to the clinical understanding of the prescriber, who is very properly concerned more with patients and populations than with drug effects (48).
Drug Utilization Studies at a Crossroads

The history of drug utilization studies shows how impressively their scope has broadened and their influence has grown. Since such studies began some 25 years ago, the drug scene has polarized strongly and its pattern has changed. Some spectacular advances apart, the pace of true therapeutic innovation has slowed substantially. That has been a consequence not of restrictive legislation but of the intrinsically limited capacity of pharmacology to provide direct solutions for diseases that are incompletely understood, and to overcome the problem posed by the non-responder. Only exceptionally does one encounter new molecules capable of modifying the natural history of their target diseases (49–53). It also remains unclear whether any substantial benefit will be derived from the new generation of antihypertensive,
Table 3. When randomization takes care of the "clinical freedom"

Problem

Does a thrombolytic treatment reduce mortality in acute myocardial infarction patients?

Criteria of recruitment and treatment

All patients with no positive and obvious contraindications are included in the trial, with no limits of age or severity of the presenting disease.

Patients are admitted and treated in open conditions, with randomization by phone to a coordinating centre, and the results are analysed accorded to the "intention to treat" criteria.

Each of the 150 participating coronary care units will apply its routine treatments to both cases and controls.

Results

12 000 patients are recruited over 18 months, representing 70% of all those who could have been admitted to the trial.

A statistically significant and clinically relevant reduction of mortality is demonstrated.

All treatments left to "clinical freedom" are found to be perfectly balanced in cases and controls.

Source: The data are based on the GISSI study (37). The same approach was followed by the ISIS-1 trial (38) and (with the exception of a double-blind condition) by the ISIS-2 (39).

Table 4. Number of patients needed to ensure the validity of population trials (example based on acute myocardial infarction)

<table>
<thead>
<tr>
<th>Statistical significance</th>
<th>No. of patients needed to show reduction in mortality:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>by 20% (from 10% to 8%)</td>
</tr>
<tr>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>0.05</td>
<td>8 589</td>
</tr>
<tr>
<td>0.01</td>
<td>12 188</td>
</tr>
</tbody>
</table>

32
Results from an overview of trials with under 50 deaths

Results from individual trials with over 50 deaths

5.4
5.7
5.8
5.9
5.10
5.11
5.12
5.14
5.15
2.1
4.1
4.3

All trials

---+--i
I
+4
I

Odds ratio (active treatment : control)

95% confidence range for trials that ran to scheduled finish

99% confidence range for trials stopped early due to good/bad trend

95% confidence range from an overview of all the trials

Source: Yusuf et al. (42).

hypolipidaemic or psychotropic drugs, whose target diseases are undergoing a major reassessment from the epidemiological and/or diagnostic points of view (54–58). More encouraging, happily, is the progress made in finding new and important uses for some old drugs (such as streptokinase, acetylsalicylic acid and nitrates, to list only examples from the cardiovascular field).
Fig. 5. Variations in the effects of treatment found in antiplatelet trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPS</td>
<td>Aspirin + dipyridamole</td>
</tr>
<tr>
<td>UK - TIA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>AICLA</td>
<td>Aspirin + dipyridamole</td>
</tr>
<tr>
<td>CCSG</td>
<td>Aspirin, sulfinpyrazone, both</td>
</tr>
<tr>
<td>Sweden</td>
<td>Aspirin</td>
</tr>
<tr>
<td>McMaster</td>
<td>Sulochtide</td>
</tr>
<tr>
<td>Toulouse</td>
<td>Aspirin + dipyridamole, Aspirin</td>
</tr>
<tr>
<td>AITIA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Toronto</td>
<td>Sulfinpyrazone</td>
</tr>
<tr>
<td>DCS</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Stoke</td>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Tennessee</td>
<td>Sulfinpyrazone</td>
</tr>
<tr>
<td>German TIA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>All cerebrovascular trials</td>
<td>Typical odds reduction 22% (SD 5%)</td>
</tr>
<tr>
<td>AMIS</td>
<td>Aspirin</td>
</tr>
<tr>
<td>PARIS - II</td>
<td>Aspirin + dipyridamole</td>
</tr>
<tr>
<td>PARIS - I</td>
<td>Aspirin + dipyridamole</td>
</tr>
<tr>
<td>Cardiff - II</td>
<td>Aspirin</td>
</tr>
<tr>
<td>ART</td>
<td>Sulfinpyrazone</td>
</tr>
<tr>
<td>CDP - A</td>
<td>Aspirin</td>
</tr>
<tr>
<td>GDR</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Cardiff - I</td>
<td>Aspirin</td>
</tr>
<tr>
<td>ARIS</td>
<td>Sulfinpyrazone</td>
</tr>
<tr>
<td>GAMIS</td>
<td>Aspirin</td>
</tr>
<tr>
<td>All myocardial infarction trials</td>
<td>Typical odds reduction 25% (SD 4%)</td>
</tr>
<tr>
<td>VA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>McMaster</td>
<td>Aspirin, sulfinpyrazone, both</td>
</tr>
<tr>
<td>All unstable angina trials</td>
<td>Typical odds reduction 36% (SD 13%)</td>
</tr>
<tr>
<td>All available trials</td>
<td>Typical odds reduction 25% (SD 3%)</td>
</tr>
</tbody>
</table>

- = Trial results and 99% confidence intervals (area of = proportional to amount of information contributed)

○ = Overview results and 95% confidence intervals

Dashed vertical line represents odds ratio of 0.75 suggested by overview of all trial results. Solid vertical line represents odds ratio of unity (no treatment effect).

Source: Antiplatelet Trialists' Collaboration (43).
In the mean time, however, the flow of "new" products of a less innovative type has by no means slowed; "me-too" drugs dominate the clinical research scene. Equally of concern is the way drugs still looking for their diseases—such as the cerebroactive compounds or "mind fortifiers" that used to be characteristic of the more southerly European countries—have not only survived but flourished; international cooperative research projects, sometimes of very dubious merit, have given such oddities a greater prominence than they probably deserve. These are areas in which market pressures have grown at least as vigorously as has the call for more stringent standards of assessment and prescribing (59).

It is fortunate that in this situation drug utilization studies, equipped with a range of complementary methods, have come so clearly to the fore, in both industrialized and developing countries (11, 60; see also Chapter 12). The basic questions that utilization studies can answer have become ever more essential: what happens to drugs when they enter the community, what factors influence their career, and what is their effect in the community (Fig. 1)?

If drug utilization research is to continue to provide reliable and useful answers that are relevant to the current situation, it will need to pursue three main objectives:

- it must seek to examine the gaps still existing between controlled experimentation and routine practice;
- it must profile the contradictions and the inconsistencies that make it so difficult to bridge these gaps;
- it must monitor the influence of polarization and conflict on the rationality and course of drug research.

While the backbone of drug utilization research will continue to be its descriptive task, a penetrating and articulate problem- and population-oriented strategy will also be needed, in which measures to ensure the quality of care must play a major role. The results of such work are bound to have a major impact on drug prescribing and the evolution of drug research. In particular, drug utilization studies can show how far actual practice deviates from the conditions under which drugs were originally studied.

To serve such a broad purpose, methods must be flexible, yet quality must be maintained; the designs and protocols employed
should, like those in other fields of research, be oriented to defined populations wherever possible. They should allow both quantitative and qualitative data to be collected and studied, for an analysis of the attitudes and beliefs of physicians and patients may be as important to full understanding as is the summation of figures (61); see also Chapter 5). One of the earliest approaches to drug utilization studies – the international approach – has retained its validity and remains a precious heritage to be maintained and developed. Periodic, cross-sectional and longitudinal studies will be required, as will studies of specific areas of relevance to public health. Finally, studies of this type may throw new light on the natural history of some diseases or problems – with or without treatment – providing us with more hard data and fewer hypotheses.

In all this work, the input of clinical pharmacology will remain vital. The clinical pharmacological tradition in drug utilization research, complementing that of other disciplines such as pharmacy and epidemiology, has brought pharmaceuticals for the first time firmly into the arena of epidemiological study; it continues to provide a firm guarantee that the discipline will remain oriented towards the needs of the patient.

Conclusions

Information on patterns of drug usage has increasingly become an indicator of the many processes that cause drugs to be chosen and taken, processes that may or may not relate primarily to the patient’s needs. In essence, a drug should always be an instrument, meticulously designed, selected and applied to deal with a well defined therapeutic or diagnostic problem. One day, we must hope, data on the use of drugs and other forms of treatment will reflect the fact that people are learning to set aside other considerations and to set course for that ideal. Until that day comes, drug utilization research will often point to and profile the discrepancy that persists between true need and therapeutic practice, and perhaps serve as a tool in correcting it.

In the course of its development over more than two decades, drug utilization research has met and linked up with such diverse disciplines and concerns as formal epidemiology, quality of care, drug evaluation and pharmaceutical auditing, as well as with cultural, social and economic research. It has evolved and, just as has been the case with randomized clinical trials, it will have to continue to grow and develop
to meet emergent needs. Drug utilization research is indeed well on the way to becoming one of the vital watch towers surveying the field of health care and leading to a greater understanding of the processes that underlie it.

References


The entire concept of therapeutic formularies is set about with controversy and, before approaching it, it is sensible to define what a formulary is — or is supposed to be. In the most generally used sense of the term, it is a limited list of drugs and their properties, intended to guide physicians in their prescribing. Most formularies are issued by institutions (such as hospitals) or by health systems within which physicians work. They are not usually a complete listing of all the drugs available; they present a selection of products, chosen in the light of their merits, their safety and their cost. It follows that a formulary can have a strong influence on physicians’ choice of products and their uses. They may find it convenient to follow its recommendations, or they may in certain circumstances be obliged to do so — for example where the formulary is issued by the body that ultimately bears the cost of prescribing.

The controversy that has arisen over formularies reflects the fact that they can be seen as part of two alternative and conflicting scenarios. In the first, formularies (and sometimes also the concept of lists of essential drugs) are viewed as an artificial and, for some, unwelcome interference in the process of free commerce and free choice. They are regarded as a reaction or over-reaction by clinical pharmacologists, a sector of the health professions or the authorities to what is conceived as the excessive influence of a powerful industry on the prescribing of medicines and on health expenditure. A vast literature has grown up to document the sometimes diametrically opposed views of the parties concerned (1–12).
In the second scenario, therapeutic formularies are viewed as a manifestation of principles that are inherent in the practice of medicine. It can be argued that the principle of universal choice is a merely theoretical ideal, and that some form of limitation is natural and normal. There is the limitation imposed by practising physicians themselves, who only employ a small fraction of the totality of the drugs available on the market, a fraction often corresponding closely to that used by their colleagues; and there is the limitation imposed by the drug approval process – the registration authorities of a country commonly reject a substantial proportion of the new drug applications they receive. Beyond that, governments, health funds and institutions usually have some form of financial ceiling on their expenditure that results in their imposing some limitation on choice. All these and similar mechanisms mean that day-to-day therapeutic practice is commonly conducted within fairly well defined limits, and that therapeutic formularies are only one manifestation of this principle and an attempt to ensure that the limits are as logical as possible.

Self-interest, money and prestige are clearly triggering factors in the virulence that has sometimes characterized the debate about therapeutic formularies; they have sometimes overshadowed what should be the dominant concern, namely the interests of the patient. The same could be said wherever the concept of essential drugs arises and is seen as a threat to the use of drugs that are not labelled as essential; even drug utilization studies have sometimes been attacked for seeming to have been designed to provide evidence of a physician’s prescribing pattern in order to persuade him or her to modify it according to standards set by others.

Therapeutic Formularies and Essential Drugs

The history of therapeutic formularies, which came to the fore as the drug market expanded, providing substantial room for selection, was already written in part when the notion of essential drugs appeared. It subsequently developed prominently under the authoritative umbrella of WHO (13).

It must be borne in mind that the concept of essential drugs was rooted in an attempt to solve the supply problems of developing countries; where drugs were available only in limited measure or not at all, it became necessary to define a basic list of drugs so important that they should as a matter of priority be made available to the entire
population. As such it was not a concept that aimed at restriction, but at expansion. The impact of the WHO initiative, formulated and outlined from 1975–1977 onwards, was far greater than expected, however. This is not the place to describe the growth of WHO's Action Programme on Essential Drugs, but one perhaps unanticipated consequence must be mentioned, for it focused attention on the incontrovertible fact that only a few of the drugs on the world market were strictly necessary to provide rational answers to most medical problems and to serve the needs of populations seeking medical care. From that point onwards, drug selection ceased to be merely a theory for debate, a measure to be imposed in situations of crisis or an instinctive part of the doctor's own self-discipline; it became proclaimed as a new and healthy way of looking at medical practice and at the significance of pharmacological interventions, seeking to give priority to those therapeutic measures that are clinically and epidemiologically essential.

The rise of this positive and creative view of the essential drugs concept strengthened the role of therapeutic formularies and provided them with a rational basis aimed at high quality of care. Above all, however, it stimulated the medical community to take positive action in the interests of good practice, while also tackling the inflation of costs and the sometimes massive duplication of products (14–15).

Table 1 summarizes the various processes of producing therapeutic formularies and essential drugs lists. The essence of the approach is clear, as is the continual potential for controversy, depending on the scenario from which one chooses to start. If one shares the view that the selection of drugs can and must be based on a careful and open-minded assessment of efficacy, safety and cost, one will readily reach a consensus with others on the essence of such a list, with only minor differences of view on particular products of closely similar merit. If, however, one's starting point is the assumption that all the drugs that have entered the market should be broadly available and accessible to every prescriber, the area for controversy may be almost unlimited.

The existing consensus might be summarized as follows.

1. There is complete and consistent agreement on the criteria to adopt to establish a therapeutic formulary or essential drugs list and on the process that should be used to ensure that the prescribing community to whom the formulary is directed accepts the choices that are made (Table 2). Once the criteria and the process have been properly set, they will in principle apply at any level of the health care system.
Table 1. Scenarios for the creation of therapeutic formularies and essential drugs lists

Drugs are included only if they provide a (new) documented means of meeting a problem/need. There is no basic difference between a national and a local/institutional therapeutic formulary; the latter is likely, however, to represent a slightly narrower selection of drugs.

Drugs are included if they are accompanied by some documentation on their pharmacological and clinical activity, without considering whether or not they contribute to health needs. There are major conceptual and numerical differences between the national therapeutic formulary (which may become a shopping list) and local/institutional therapeutic formularies and essential drugs lists.

As a national health system develops it tackles progressively more problems/diseases and therefore adopts all the drugs that provide appropriate answers. The therapeutic formulary is the essential drugs list for that health system.

A national health system does not exist. Health and drugs are market goods that may be bought by those who have sufficient means. Therapeutic formularies, essential drugs lists and policy do not exist at the national level, though local and institutional initiatives may be taken.

For administrative or economic reasons, an authority decides that under its jurisdiction only a restricted number of the marketed drugs will be reimbursed to the users. The selection of such a list may or may not meet the criteria of a therapeutic formulary or essential drugs list.

2. Although the criteria and process are applicable at all levels, the end result will vary with the health care situation in which they are applied. Because of the different needs in the referral populations, a hospital-oriented formulary or list will thus clearly differ from one intended for use in ambulatory or primary health care; both the number and nature of the drugs included are likely to be different.

3. The central and decisive goal of any therapeutic formulary or essential drugs list is to favour rational prescribing in the specific situations for which it is intended. Financial or administrative considerations (costs, management problems) may play a secondary role but must not impair the basic aim of providing effective and safe therapy.
Table 2. Ideal criteria and procedures for establishing a therapeutic formulary or essential drugs list

<table>
<thead>
<tr>
<th>Criteria for drug selection</th>
<th>Procedures</th>
</tr>
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<tbody>
<tr>
<td>A drug should have proven therapeutic efficacy (not only pharmacological activity) in controlled human experimentation</td>
<td>A commission is established consisting of qualified representatives of the administration, of the medical profession, of the pharmacists and of nursing staff</td>
</tr>
<tr>
<td>A favourable benefit/risk profile should exist</td>
<td>A draft (prepared ad hoc or developed from existing texts) is circulated for broader comments and reactions</td>
</tr>
<tr>
<td>Fixed-dose combinations should have specific and documented advantages over single components</td>
<td>The final contents are decided through a series of intensive meetings, where ad hoc documentation may be requested to solve controversial problems</td>
</tr>
<tr>
<td>More than one drug may be recognized for the same indication only where this is necessary to allow flexibility and second choices for particular patients</td>
<td>The therapeutic formulary/essential drugs list is presented to its users, and programmes of information and training are started to support the policy</td>
</tr>
<tr>
<td>Motivated requests to use drugs outside the basic list for individual patients may be evaluated</td>
<td>Periodic evaluation of proposals for modification or extension of the list is ensured</td>
</tr>
<tr>
<td>Investigational or doubtful drugs may be admitted for use in treatment only as part of controlled studies</td>
<td>Full revision and updating is advisable every three years, to care for specific drug changes and broader adjustments of therapeutic strategies</td>
</tr>
<tr>
<td>Cost considerations are decisive for therapeutically equivalent drugs</td>
<td>Careful evaluation of cost as related to efficacy and safety is undertaken</td>
</tr>
</tbody>
</table>

4. The number of drugs included in such a selection, whether at the country or institutional level, is less important than the consistency of the criteria adopted to choose them. Provided the criteria listed in Table 2 are observed, differences between national lists will reflect primarily differing traditions in medicine and culture, but within a scientifically acceptable range of variation; in one part of Europe, for
example, physicians may feel they need rather more choice of nonsteroidal anti-inflammatory agents than in another, but be content with a smaller range of treatments for hypertension.

5. A policy based on selection will be very difficult to implement in countries where the criteria for drug registration do not comply with the criteria cited in Table 2, since the first and basic selection at the regulatory level will not have been logical.

Therapeutic formularies and essential drugs lists for special situations have come into existence in a range of countries with different economic status, medical traditions and drug legislation (Table 3). This provides important material for comparative study; the selections made can throw a useful light on the basic concepts of how medicine should be practised and on current concepts of the term essential in this context. The essential drugs concept was originally developed to tackle with some dignity and logic the problems of desperate poverty and deprivation in developing countries, yet, even in meeting that emergency, national and regional concepts of what was essential differed markedly, and the WHO model list of essential drugs provided no more than a starting point for discussion. As communities advance beyond mere subsistence level, these differences in attitude and need remain very clear. The range of drugs that must be considered vital to a community will vary both with the actual prevalence of particular disorders and with the views of how these can best be prevented, diagnosed and treated. These are the central elements determining the drugs a community wants; availability of economic resources and other administrative considerations are only secondary factors in determining what can be provided or what will in practice be recommended. Even allowing for existing constraints (and no country is entirely free of financial or other constraints) one can still put the health interest in the middle of the picture. To be acceptable from a health point of view, the choices must give priority to the needs of most of the population and to those treatments that are most likely to protect or improve the health of that population effectively.

Viewed in this way, an approach based on the idea of essential drugs is simply the application to the field of pharmaceuticals of a scientifically sound health policy. It must not (and probably cannot) be established or maintained for purely economic reasons; it demands the existence of a healthy view of medicines and prescribing, shared by health workers and the community. In that respect there is a close
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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| 1970 - 1975 | Development and evaluation of hospital formularies in Italy and the United States  
Systematization of the commented texts of national drugs lists in Scandinavian countries  
First lists of essential drugs in developing countries (such as Mozambique and Peru) |
| 1978 | WHO Declaration of Alma-Ata on Primary Health Care  
Publication of WHO Regional Office for Europe's first book on drug utilization studies (WHO Regional Publications, European Series, No. 8)  
A formulary (with commentary) for general practice written with general practitioners and published in Italy |
| 1980 | Creation of WHO Action Programme on Essential Drugs |
| 1981 | Creation of the periodic British National Formulary |
| 1985 | After long debate, approval of limited lists of drugs in the United Kingdom for use by general practitioners  
In the first half of the 1980s, publication of various commented, problem- or drug-oriented therapeutic formularies for general practice, in, for example, Belgium, Nicaragua, Scandinavia, Spain (starting from Catalonia) |
| 1988 | Fifth edition of the list of essential drugs  
Clear and growing acceptance of commented formularies for general practitioners and local practices in most developed countries  
Availability of commented formularies in many of the least developed countries (such as Burkina Faso, Ghana and Zimbabwe) |

A relationship between a therapeutic formulary and an essential drugs list. At whatever level they are introduced, both will tend to reflect the same health needs, the same attitudes, the same cultural elements, and the existence of the same constraints; and both will, at their best, reflect a logical approach to that complex of factors.
Drug Utilization Studies

The development of the twin concepts of therapeutic formularies and essential drugs lists is one of the major reasons for studying drug utilization. In establishing a selected list of drugs one will, after all, need to be guided to an important extent not only by epidemiological statistics and scientific considerations of efficacy and safety but also by current patterns of usage, which are likely to reflect what the community wants and needs. In some areas, when one sets out to make a selection, the basic data required on current patterns of drug utilization will be lacking or inadequate, and further research will be required. That research will need to be undertaken not only nationally but also at specific levels of health care, such as hospital, outpatient or general practice, so that the current needs and attitudes at all those levels are profiled as clearly as possible. What is more, the research must continue, so that the selection of drugs can be adapted from time to time to meet shifts in the pattern of disease, in the way in which medicine is practised, and in the spectrum of drugs and knowledge available. Drug utilization research will form an important counterbalance to the administrative and economic influences that may otherwise distort drug supply, and it prevents a petrification of policies. It also facilitates the examination of criticism that such lists make it impossible to meet valid needs (Table 4). Such research, some examples of which are given in Table 5 (see also 16–18), will also ensure that the effort to provide selected lists of drugs remains credible and acceptable. In fact, the very first WHO report on the use of essential drugs, issued in 1977 (13), listed drug utilization studies and drug selection programmes alongside one another as vital elements in the establishment of sound pharmaceuticals policies.

Drug utilization studies, designed to produce a tool in the development of high quality formularies and essential drugs lists, would seem to be a priority for the growing number of pharmacists who see the assessment of the quality of therapeutic care and an epidemiological approach to drug evaluation (both in and outside the hospital) as a most promising field of study. The involvement of pharmacists in such work will help to develop their acceptance in the clinical field without compromising their identity, for it will produce data of direct relevance to problem-oriented information programmes and assure a firm basis for a constructive dialogue with doctors and nurses (19).
Table 4. Situations in which therapeutic formularies and essential drugs lists do not meet genuine needs

<table>
<thead>
<tr>
<th>Situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected drugs are not available</td>
</tr>
<tr>
<td>No consensus exists between the choices of the commission and the cultural background or practice of the prescribers</td>
</tr>
<tr>
<td>Selected drugs are not used according to rational criteria, and patients do not receive appropriate treatment</td>
</tr>
<tr>
<td>Random or recurrent &quot;negative&quot; outcomes are attributed to the limitation of drug choices and create a situation of conflict</td>
</tr>
<tr>
<td>Administrative rigidity prevails over technically sound criteria for management and updating</td>
</tr>
</tbody>
</table>

Table 5. Drug utilization studies that can support therapeutic formularies and essential drugs lists

<table>
<thead>
<tr>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative assessment of the clinical consequences of different drug choices or strategies in similar settings</td>
</tr>
<tr>
<td>Examination of criticism, such as allegations that a therapeutic formulary/essential drugs list policy results in a failure to meet needs, in dissatisfaction or in uneasiness among prescribers</td>
</tr>
<tr>
<td>Prospective comparative study of the benefit/risk and benefit/cost ratios of different therapeutic interventions in well defined populations exposed to different drug choices</td>
</tr>
<tr>
<td>Evaluation of drug choices made in practice by general practitioner groups in different countries as related to their market and cultural backgrounds, and to the overall management strategies adopted for their patients</td>
</tr>
<tr>
<td>Surveillance of the evolution of an essential drugs list policy in different primary health care settings and of its relationships to the evolution of the health care system of the countries concerned</td>
</tr>
</tbody>
</table>
The clinical pharmacologist, too, can be involved; the creation of close links between drug utilization studies and ventures in drug selection—whether through formularies or essential drugs lists—is one of the key strategies proposed by a working group of the WHO Regional Office for Europe to promote rationalization in primary health care and to give clinical pharmacology concrete opportunities to monitor its impact on the quality of prescribing (20).

References


The development of important methodological tools for drug utilization studies at the beginning of the 1970s rendered possible much comparative international and interregional research. Developments and opportunities arising in more recent years have, however, created a need for new strategies and experimental methods in this field.

If drug utilization studies are to be reliable, they will have to adhere to strict methodological standards, the most basic of which continue to be the use of a common drug classification system and of an international unit of measurement.

Drug Classification Systems

The need for a single international classification system as a tool for performing comparative studies of both supply and consumption was felt from an early phase of drug utilization research. Such a system would provide the only solid basis on which to compare the situation between countries and periods of time, and would be essential if consumption data were to be correlated with other types of drug information, such as that relating to the incidence of adverse reactions (1).

Medicines can be classified in various ways: according to their mode of action, the pharmacological or therapeutic groups to which they belong, according to their indications, or according to their structure. A pharmacological/therapeutic classification would, for instance, regard analgesics, antacids, anti-arrhythmics, anti-infectives, anticoagulants and diuretics as primary groups. A classification according to indications would group medicine under such headings as
hypertension, arthritis and rheumatism, diabetes, or bronchitis. Each such classification type has its own advantages and limitations and the usefulness of each one will depend on the use to which it is to be put.

Of the various systems proposed and used experimentally over the years, only two have survived and attained a dominant position in drug utilization research: the anatomical-therapeutic (AT) classification and the anatomic-therapeutic-chemical classification (ATC), which was in principle derived from it.

The anatomical-therapeutic (AT) classification system
The AT classification system is used by the European Pharmaceutical Market Research Association (EPhMRA) and by the International Pharmaceutical Market Research Group (IPMRG). It has been adopted by various European and American countries, and it is also used by IMS (International Marketing Services) which conducts surveys for the pharmaceutical industry.

Drugs are divided into 14 main categories, according to the system or to the organ on which they act, such as the alimentary system and metabolism, the blood and blood-forming organs, the heart and vascular system or the central nervous system. The first letter in the code allocated to a drug refers to the system in which drugs act; four more digits follow, corresponding to second and third levels of classification. For instance, the N group (central nervous system) is split into therapeutic subgroups (second level), and each one of these into more pharmacological subgroups (third level). Diazepam is, for example, classified as follows:

\[
\begin{align*}
N & \quad \text{Central nervous system} \\
 & \quad \text{(first level, anatomical group)} \\
N05 & \quad \text{Psycholeptics} \\
 & \quad \text{(second level, main therapeutic group)} \\
N05A2 & \quad \text{Tranquillizers} \\
 & \quad \text{(third level, therapeutic subgroup)}
\end{align*}
\]

When a pharmaceutical speciality is a fixed-dose combination containing two or more active ingredients, it is classified according to its main therapeutic use. A product, for instance, containing an analgesic and a tranquillizer but used primarily to ease pain is usually classified as an analgesic, without reference to its tranquillizing component.
Two main problems arise with the use of such a classification. The first is that it does not allow the identification of a particular drug. For instance, all tranquillizers (benzodiazepines, diphenylmethane derivatives, glycol derivatives, etc.) are classified in the same group (N05A2), and it is impossible to recognize specialities containing, say, diazepam, since the lowest level of classification, the third one, is a therapeutic rather than a structural subgroup. The second limitation arises with the classification of fixed-dose combinations. As these are classified according to their main indication, they may contain one or more components that remain unclassified and, as it were, hidden from view, as in the example cited above. This can militate against the use of this classification system in drug utilization studies. If a study on the use of psychotherapeutic drugs fails to detect those that are present in fixed-dose combination with analgesics and classified therefore in the N02B1 subgroup, the consumption will be underestimated. The difference is not negligible. In Spain in 1980, the total consumption of psychotherapeutic agents amounted to 65.7 DDD (defined daily doses) per 1000 inhabitants per day; pharmaceutical specialities classified as psychotherapeutics, however, only accounted for 42 DDD per 1000 inhabitants per day; most of the remaining psychotropic drugs were included in fixed-dose combinations with analgesics (N02B1) (2).

**Anatomical-therapeutic-chemical (ATC) classification system**

The ATC classification system is derived from the AT concept; essentially it was developed by the Norwegian Medicinal Depot and involved the addition of two further levels of classification, so as to allow for the complete chemical and therapeutic identification of each compound. The system was initially used most extensively in the Nordic countries – Denmark, Finland, Iceland, Norway and Sweden (3) – but, as pointed out already, it was later adopted by the WHO Drug Utilization Research Group (DURG) through which it has been used in many other countries. Again one may take as an example the classification of diazepam:

- **N** Central nervous system  
  (first level, anatomical group)
- **N05** Psycholeptics  
  (second level, main therapeutic group)
- **N05B** Tranquillisers  
  (third level, therapeutic subgroup)
Benzodiazepine derivatives
(fourth level, chemical/therapeutic subgroup)

Diazepam
(fifth level, chemical substance subgroup)

In this system, as in the AT approach, a fixed-drug combination will be classified basically according to its main indication; fixed combinations are usually distinguished from plain preparations, however, by the use of a parallel fifth level classification, usually employing the 50 series:

Diazepam
Diazepam, combinations

In addition, combined preparations that contain psycholeptic drugs and are classified in groups other than N05 (psycholeptics) and N06 (psychoanaleptics) are classified separately at level 4 or 5, usually using the 70 series:

Acetylsalicylic acid
Acetylsalicylic acid, combinations, excluding psycholeptics
Acetylsalicylic acid, combinations with psycholeptics

For further information and guidelines for the ATC classification, the reader is referred to Nordic statistics on medicines 1981–1983. Part 3: guidelines for ATC classification (3).

Units for the Quantification of Drug Use

Before an international unit of measurement of consumption was agreed on, the consumption parameters most widely used in drug utilization studies included cost (for example, the overall cost or unit cost of a drug, or consumption expressed in terms of economic expenditure by a particular institution), numbers of units (for example, tablets or packages) dispensed or sold, prescriptions (expressed in numbers or mean costs) and overviews of the sales of “top” products.
All these parameters have some limitations when comparing consumption at the international level, but they can nevertheless be useful, and they deserve some consideration here.

**Cost studies**

Cost studies produced the first “drug statistics”. They were carried out mainly by public health organizations to monitor expenditure on drugs. The quantification of drug consumption in economic terms can indeed be useful in evaluating some aspects of general health policy in a given country, particularly if drug expenditure is examined as a proportion of total health expenditure.

If drug expenditure is to be compared between countries, it is best expressed in relation to income per head. An expenditure of US $30 per year in a country with an income per head of US $3000 will need to be viewed in a different light from the same absolute level of expenditure in a country where the per head income is US $8000 (4,5).

Clearly, considering consumption in economic terms provides no exact notion of the quantity of drugs sold or consumed, or of the “relative therapeutic intensity” (i.e. the intensity of drug exposure) within the population (6). A study by Baksaas & Lunde on sales of antihypertensive drugs in Norway in 1971–1978 (see Fig. 1) shows the consequences of choosing a cost unit as compared to a quantity unit. Prices of medicines differ very much over a period of time in the same country, and they also vary, sometimes markedly, from one country to another. Furthermore, the prices of medicines follow more complex rules than those of any other product (1). The priorities adopted by the health system, the registration policy, the patents situation and the costs in the country of origin are among the particular national policy elements that can have a direct influence on pharmaceutical prices.

**Studies bases on numbers of units sold**

Consideration of consumption in terms of “packages sold” gives a more precise idea of drug consumption than does economic value. This unit too has its limitations, however, notably when one is studying the evolution of consumption over a period of time or comparing consumption between countries. One package or unit could be a container of 15 tablets, one of 40 tablets, a box with 10 suppositories, or a set of 10 ampoules of the same drug in a long-acting injectable form. In 1987, for instance, the Spanish pharmaceutical market had at least 38 different brand names of diazepam in 67 pharmaceutical
Comparing total unit cost with total number of defined daily doses

Comparing subgroups of drugs in terms of unit cost and defined daily doses

Source: Baksaas & Lunde (6).

forms, ranging from drops containing 2 mg/ml to packets containing a total of 500 mg or sets of six 10-mg ampoules (7); in other parts of Europe, the same product was no doubt available during that same year in yet other forms, strengths and packaging sizes, and in any country these are likely to change as time goes by. Under these conditions, there may be little point in comparing numbers of packages sold in different countries and/or different periods of time – indeed, it can prove entirely misleading to do so.

Prescriptions
The number of prescriptions issued, such as from a health institution or in a given geographical area, has similarly often been used as a
measuring unit, and it may reflect the physician/patient relationship and its variations over a period of time. The number of drug units (or drugs) prescribed per prescription may vary widely, however, and this must be corrected for if the raw data are to be interpreted in terms of therapeutic exposure (8). In general, this cannot be done properly unless the investigation includes the diagnosis and other relevant considerations. Unfortunately, this information is often difficult to obtain for reasons of confidentiality; such an analysis may also interfere with the situation, and investigations of this sort are usually expensive (1).

The Defined Daily Dose System

To overcome the limitations of expressing consumption in terms of costs or of units prescribed or sold, a new unit of measurement was established and has come into widespread use: the defined daily dose (DDD). This is the unit used by the Nordic Council on Medicines and it has now for many years been recommended by the DURG as a unit of measurement for comparative drug consumption statistics (9).

Definitions

A DDD is defined for each drug (i.e. each active ingredient); the defined dose corresponds to what is assumed to be the average dose per day for the drug, when used in its main indication (3). A DDD is allocated to a drug by the Nordic Council on Medicines, working in close association with the WHO Regional Office for Europe in Copenhagen.

The DDD is no more than an arbitrarily chosen technical unit for the measurement of drug consumption, and it makes no pretence of providing a therapeutic recommendation. It is as close as possible to prescribing reality, however, and it is established in the light of recommendations in the literature, the manufacturer’s advice in the data sheet, and experience gained in the field with the product concerned.

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

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

Consumption in a given geographical area is usually expressed in DDD per 1000 inhabitants per day, as was done in the examples given earlier in this chapter. This parameter provides a rough idea of the proportion of the population receiving a standard drug treatment every day. It does not indicate how many patients are actually being treated, however, except in the case of drugs used continuously (such as insulin or contraceptives). For example, a consumption level for an antibiotic or analgesic of 15 DDD per 1000 inhabitants per day theoretically corresponds to 1.5% of the population on continuous treatment; but such drugs are more generally used over short periods, and the reality is probably closer to 15% of the population taking the drug for a month or 60% for a week. In such cases, consumption is better expressed as DDD per inhabitant per year, making it easier to visualize what the figures mean in real terms (10).

The experienced drug utilization researcher soon learns the scope and limitations of this approach. Some of these are considered below, but at this point it may be instructive to provide some examples of calculations that the system renders possible.

**Calculation**

In some situations, data will be available on the number of units of a drug sold. In that case, the number of DDD consumed is calculated according to the following formula:
Amount of drug sold in one year (mg) \times 1000 \text{inhabitants} = \text{DDD}/1000 \text{inhabitants/day}

\[
\text{DDD} \quad (\text{mg}) \times 365 \\
\text{days} \times \text{number of inhabitants}
\]

For example, the DDD of diazepam is 10 mg; if 300 million 5-mg tablets of diazepam are sold in one year (365 days) in a country with 37 million inhabitants, the consumption will be:

\[
\frac{5 \times 300 \text{ million}}{10 \times 365 \times 37 \text{ million}} \times 1000 \text{inhabitants} = 11.1 \text{DDD}/1000 \text{inhabitants/day}
\]

This figure means that on average 11.1 out of 1000 people (or 1.11\%) will be using a dose of 10 mg diazepam every day.

Consumption in hospitals is calculated in the same way as consumption in the general population, but it is usually expressed as the number of DDD per 100 bed-days; in making the calculation, the days of admission and discharge are usually counted together as one bed-day \((11)\). The following formula is applied for the calculation of the consumption in a hospital:

\[
\frac{\text{Number of units delivered in a fixed period (mg)} \times 100 \text{ beds}}{\text{DDD} \times \text{Number of days in the period} \times \text{Number of beds} \times \text{Hospital occupancy index}} = \text{DDD}/100 \text{ bed-days}
\]

For example, in a hospital with 326 beds and an occupancy index of 93\%, 3912 tablets of diazepam (5 mg) have been delivered in one year (365 days). As the DDD for diazepam is 10 mg, the consumption of diazepam will be:

\[
\frac{5 \times 3912 \times 100}{10 \times 365 \times 326 \times 0.93} = 1.78 \text{DDD}/100 \text{ bed-days}
\]

Consumption in hospitals expressed in this way gives a rough estimate of the proportion of patients treated with a given drug during a certain period.

**Limitations**
The introduction of the DDD unit has meant a great improvement in the measurement of drug consumption, but some problems and limitations
still remain and they must be considered when interpreting these data. Some of these problems are common to all countries and others are primarily important in countries with a high proportion of fixed-dose combination products.

To begin with it must be emphasized that studies in drug consumption using the DDD methodology use data on units issued or sold, and it is well known that not all drugs reaching the patient are necessarily consumed. It is also important to consider, and adapt if necessary the size of the population used as a denominator; usually general consumption is calculated for the total population (all age groups) but drug use is often concentrated within certain specific groups (for example, antihypertensives, oral contraceptives, some vaccines and fluoride preparations) and it can be more meaningful to take such a group as a denominator. The consumption, for example, of oral contraceptives is routinely given as the percentage of women 18–44 years old using these preparations (12).

In the simplest situation, i.e. where drugs are used continuously and for one indication only, the consumption given in terms of DDD per inhabitant may roughly agree with the morbidity figures (13–15). This has been proven to be true for antidiabetic drugs, and particularly for the oral hypoglycaemic agents (16). By contrast, one cannot expect such a correlation for drugs used in several indications (such as benzodiazepines or antipsychotics) or in short and variable courses of treatment (such as analgesics or antibiotics).

Furthermore the DDD, as a technical unit of measurement, is not necessarily equivalent to average doses actually prescribed (prescribed daily dose (PDD)) nor yet to the average dose actually ingested every day. The doses prescribed and taken in a particular community will vary with the indications actually predominating, national or regional therapeutic traditions, and with the attitude of patients. For certain purposes therefore, and particularly where one is anxious to profile these variations in actual patterns of use, the PDD has been introduced as an additional unit that can be used alongside the DDD; the PDD represents the average prescribed dose in the main indication. The new unit has been used in several studies. These show that although the difference between the DDD and the PDD is for some drugs quite small (such as antihypertensives and antidiabetics) (17), it may be appreciable in other fields of therapy (such as analgesics and psychotropic agents) (18).
The DDD methodology does not provide a means of profiling the extent to which fixed combinations are used (16, 19). Although a specific unit has been defined for combined preparations—the effective dose (ED)—it is not suitable for comparing the consumption of drugs between countries if different types and doses of fixed-dose combination are in use; such comparisons can, however, validly be made for some widely accepted and standardized fixed combinations, such as those of estrogen and progestogen, trimethoprim and sulfamethoxazole, or levodopa and a decarboxylase inhibitor. Any broader international comparison of the use of fixed combinations will demand further data on the consumption of each of the active ingredients, in addition to the number of units or the number of ED sold, and these data may be difficult to obtain. In countries with a high proportion of combined preparations, it will be easier to express consumption in DDD, stating which proportion comes in combined preparations. In this way the total consumption of a given drug, or of a given pharmacological or therapeutic group of drugs, can be validly compared between countries with different drug markets (2).

Methods Used in Qualitative Studies

The fact that a drug is widely used does not mean that good treatment is being provided; the intrinsic value of a drug does not necessarily bear any relation to its expected degree of use (20).

To study and compare not merely the volume of prescribing but also its quality and content, one will need to extend one's methods and units to take into account such concepts as to the "potential therapeutic value" or "intrinsic value" of the drugs used, as well as to have some means of allowing for safety and adverse effects. Methods have been developed for this purpose, and modified in the light of experience so that they can be used for international comparisons (21). The parameters used in qualitative studies can be defined as follows.

The potential therapeutic value

The potential therapeutic value of a drug can be reasonably classified under four headings:

(a) high potential therapeutic value, covering products whose merits have been amply confirmed in published works, or whose value is beyond any doubt for other reasons (such as insulin for acute juvenile diabetes or vitamin C for scurvy);
(b) *relative/irrational therapeutic value*, covering products that, while having an active component, are less valuable and logical because some illogical component is also present (such as an unnecessary vitamin or co-enzyme);

(c) *doubtful/no therapeutic value*, covering products whose therapeutic efficacy has not been demonstrated conclusively, even in one indication, because the active component has never been conclusively proven to be effective, or the product contains an active ingredient in a dose that is insufficient to serve its intended purpose;

(d) *unacceptable*, covering products that have a clearly unfavourable benefit–risk ratio under all circumstances.

**The expected degree of use**

This classification is applied only to those products that have been classified as being of high potential therapeutic value. The classification comprises two groups. Drugs with a *high expected degree of use* have recognized therapeutic efficacy in prescription situations that frequently recur. Those with a *relative expected degree of use* include drugs of recognized therapeutic efficacy, whose use is, however, likely to be limited for some reason, such as because:

(a) a better alternative exists (for example, chloramphenicol for indications other than confirmed or suspected meningitis caused by *Haemophilus influenzae*);

(b) they are basically suitable only for hospital use (such as some cephalosporins and aminoglycosides);

(c) they are likely to be prescribed chiefly by consultants to carefully monitored patients (such as chemotherapeutic agents against cancer, clofibrate or oral anticoagulants);

(d) they are indicated only in very unusual circumstances (such as vitamin C for scurvy).

**Types of Drug Utilization Study**

For historical reasons, the earliest drug utilization studies were quantitative, descriptive and inspired largely by considerations of cost, and
most of them were undertaken in the Nordic countries, in Czechoslovakia and in Northern Ireland. Qualitative and analytical studies and the extension of the work into other parts of Europe and the world came later (17, 22–25). The need to tackle the field broadly is reflected in the definition of drug utilization work adopted by WHO (26): studies of “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences”. Only such a broad approach will be useful in arriving at a valid therapeutic audit (27). Some of the types of study required will be outlined below.

**Studies of supply**

Studies of drug supply in different countries have shown very wide differences (see Table 1), no doubt attributable in part to varying national policies on drug registration and control. There is, however, probably an interaction in both directions between drug control and professional practice: the regulatory tradition may reflect national concepts on the proper place of drugs in medicine, and conversely the control system itself will, by modifying the range of drugs available, influence the way in which patients are treated (5).

Studies on drug supply may also usefully highlight the way in which medicines are marketed and presented to the health professions and the public, and examine both the influence of this information flow and the extent to which it varies between countries.

Supply studies in the above sense are relatively simple to undertake yet they can be of immediate value, even where quantitative studies of utilization have not yet proved feasible (Table 1). They provide clues to the factors that influence consumption; they can also provide feedback to policy-makers and regulators that helps them understand the repercussions of their activities, particularly when viewed in international perspective. Striking findings have, for example, emerged in simple studies of the availability of nonsteroidal anti-inflammatory drugs (28), comparisons of the range of psychotropic drugs marketed in different countries (2), and overviews of the numbers of pharmaceutical specialties registered in one year (29).

Sources of information used in such studies include: national registers of pharmaceutical specialties maintained by health systems or regulatory agencies, and catalogues of marketed pharmaceutical specialties prepared by sickness funds, professional associations, the pharmaceutical industry or other bodies.
Table 1. The pharmaceuticals market in three Nordic and two southern European countries

<table>
<thead>
<tr>
<th>Items on the market</th>
<th>Number of items in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredients</td>
<td>730</td>
</tr>
<tr>
<td>Trade names</td>
<td>1,040</td>
</tr>
<tr>
<td>Pharmaceutical forms</td>
<td>2,058</td>
</tr>
<tr>
<td>Fixed-dose combinations*</td>
<td>10–15%</td>
</tr>
</tbody>
</table>

*Figures here represent market shares.

Quantitative studies of drug consumption
The quantitative studies with which much drug utilization work began were essentially an attempt in government and professional circles to obtain the same type of drug utilization figures that had long been available to the pharmaceuticals industry on the basis of its own market research or the services provided by such organizations as IMS.

Quantitative studies may provide overall statistics, commonly with a detailed breakdown, or specific data in a given situation. It is generally wise to ensure that information obtained through one channel is confirmed by data obtained in a different manner, at least in the form of spot checks. Sources of information variously used include:

(a) sales data obtained by privately owned companies that carry out surveys through a sample of pharmacies; the most prominent service is that provided exclusively to industry by IMS and generally not available to others;

(b) official figures from sickness funds and health services, obtained as part of costing and reimbursement activities;

(c) prescription data, similarly obtained from health services or locally (for example, through hospitals or group practices).

Most accessible data relate to prescribed products. Utilization figures for products used for self-medication are generally not known.
in detail, although sometimes a general estimate can be obtained by subtracting overall prescribing figures from the totality of industry sales (30).

The quantitative studies seen showed that international comparisons could provide some surprises. Studies comparing trends in the use of certain groups of drug (antidiabetics, psychotropics, anti-hypertensives) in a range of countries have shown differences that are difficult to explain purely in terms of a differing prevalence of the diseases concerned (23–25, 29, 31–33). Such comparisons can suggest areas of medicine in which drugs are being used inappropriately or to excess.

Even purely national studies of this type can prove useful, however, notably in identifying differences in treatment within a country (31, 34), in evaluating the effects of regulatory measures and information campaigns (35, 36) and in undertaking benefit–risk analyses (37–39).

**Qualitative studies**

Identifying even wide differences in the supply or use of drugs between countries or areas of a country does not necessarily indicate which of the various patterns identified is the preferred one. The data may in any case need to be further refined before one can even consider any qualitative assessment. If, for instance, the consumption of a particular group of drugs is higher in one location than in others, one will need to determine precisely what is being used to excess and in what form; fixed combinations may be in wide use as may specialities with an inadequate concentration of active component, or poorly formulated products. Sometimes the over-prescribing will reflect gross overuse of one product or in one area of the country, thus narrowing the scope of further enquiry.

The sources of information that must be tapped for qualitative studies are essentially the same as those used in quantitative studies, but supplemented by sources providing a reliable assessment of the efficacy and safety of the products concerned.

Studies of prescribing quality are better developed at the national level than the international level and some results are available on the quality of supply (40) and on the quality of the most widely prescribed drugs (20). Again, the findings can be spectacular and of direct value in formulating creative policies. In Spain, for example, 41% of the medicines consumed in 1981 were found to be of high potential value.
and 12% were of relative value; of the remainder, however, 25.5% were of doubtful or no value, and 21.4% were rated as unacceptable (20).

The quality of supply can also be compared with the quality of consumption within the same country, to see how each changes with time. The quality of the psychotropic drugs consumed in Spain in 1980 was, for example, found to be higher than the quality of the drugs supplied (2), in other words the prescribing physicians tended to select the drugs of greater value. Nevertheless, a comparison of the quality of the most prescribed drugs (20) with the quality of prescribed psychotropic drugs in the same year showed that, whereas the consumption of pharmaceutical specialities of high intrinsic value was almost the same in both samples, the consumption of products classed as unacceptable was twice as high in the psychotropic group as in the product spectrum as a whole (2).

A relatively recent study has compared the quality of the most widely prescribed drugs in 17 European countries; this is the largest international study carried out in Europe to date. Besides showing wide variations in the quality of the most prescribed drugs, it also provides interesting evidence that the lists of the top 50 prescribed drugs, which are fairly readily accessible, give a fair impression of the main features of a pharmaceutical market (21).

**Studies of prescriptions and prescribing**

The studies described up to this point, however useful they may be, provide no in-depth insight into the behaviour of prescribers and patients. For that, one needs to complement them with investigations of prescription habits and compliance and with data culled from patient interviews.

Studies of prescription practices have a long tradition in the Nordic countries (13, 15, 35, 41–43), the United Kingdom (31, 44) and in some other parts of the world (36, 45, 46). Data on prescriptions are commonly accessible as a result of the reimbursement activities of health services, which make it necessary to undertake costing and make payments for drugs supplied to the individual patient. In Spain, for example, all prescriptions issued within the social security system are fully processed and stored in a database (47). This type of material can have its limitations, since it is collected primarily for administrative purposes and may lack essential details; however, it can be complemented by other data, obtained for example from hospitals (11, 48, 49),
from local authorities \((34, 50–52)\) or from the review of medical records \((42, 53)\), and surveys of sample prescriptions can be undertaken, as in Sweden \((41, 43)\).

In the Swedish county of Jämtland, where prescribed drugs dispensed to 13% of the inhabitants have been continuously recorded since 1970, long-term in-depth studies are possible. Individual patients are fully identifiable by their national identity number so that they can be followed up for studies on the indication for drug use, the incidence and nature of side effects and compliance with the prescribed drug regimen \((8, 41)\).

Using data on prescriptions and prescribing, it is possible to relate prescribing patterns to many other matters. One can, for example:

- analyse patterns of drug use among patient categories defined by age, sex or diagnosis \((43)\);
- study the relationship between the prescribed medicine and the apparent indication;
- identify the illnesses most frequently treated;
- identify and study prescription determinants, such as the extent to which prescribing has been influenced by particular information or publicity campaigns \((54–56)\);
- examine specific safety problems in drug use in the light of actual practice \((37–39)\).

**Studies of patient compliance**
The term compliance has been defined \((57)\) as “the extent to which the patient’s behaviour (in terms of taking medications, following diets or executing other life-style changes) coincides with clinical prescription”. Various studies show that only a (variable) fraction of the patients who are prescribed drug treatment actually do take it, though few studies have focused on the determinants of compliance \((58–60)\). The relevance of this issue to drug utilization studies as a building block for drugs policies is evident; incorrect use can undermine the wanted effects of a drug, aggravate its adverse reactions and generally involve wastage of resources.

Traditionally, the sources of information for the measurement of drug compliance have fallen into two main groups \((61, 62)\), according to the techniques used to collect it. Indirect techniques include noting
clinical outcome, detecting physiological markers, recording the
cjudgements made by physicians, carrying out structured patient inter-
views, controlling repeated prescriptions, counting pills and moni-
ring medication (63). Direct techniques comprise methods such as
measuring the level of a drug or its metabolites in blood or urine.

Ad hoc studies
Alongside all the techniques for drug utilization study that are of
general application, some will always be developed to meet a particular
need or exploit an unexpected opportunity.

When, for example, generalized utilization studies in Scandinavia
and Northern Ireland revealed differences in the use of antihypertensive
and antidiabetic drugs, it obviously became necessary to look both
for explanations and for consequences. A questionnaire survey was
therefore undertaken in a random sample of 400 general practitioners
and hospital doctors (64, 65). The physicians were asked to give their
opinion on the choice of therapy for three model cases designed to
cover the spectrum of treatment of type II diabetes – from diet alone to
insulin – and on the choice of antihypertensive drugs for analogous
case histories relating to mild or moderate hypertension. In the case of
type II diabetes, the results showed significant differences in the
approach to treatment between physicians in the three places studied
(Northern Ireland, Norway and Sweden). These differences related to
the choice of drugs, however, rather than to the threshold for starting
drug treatment. The results also suggested that important differences
may exist in the prevalence of clinically recognized type II diabetes
(64). With respect to antihypertensive drug use, the study revealed
differences in the propensity to start antihypertensive therapy in North-
ern Ireland and in Norway and Sweden. The study also indicated that
the lower prescribing of antihypertensives in Northern Ireland and, to
some extent, in Norway, as compared to Sweden, might be due to
differences in true or apparent morbidity (65).

Ad hoc studies may also be designed to focus on drug treatment
patterns in particular population groups, for example, determined by
age (66–68). Knowledge of drug use in population subgroups (such as
pregnant or lactating women) is surprisingly limited, but an interna-
tional collaborative study of drug use in pregnancy has been set up by
WHO and data are now emerging.
References


The quantification of drug risks in practice

D. Lee & U. Bergman

When considering the methods and usefulness of drug utilization studies, some attention should be devoted to monitoring adverse reactions. One of the major problems about studying the side effects of drugs has been determining their frequency. To do this, one must have both a numerator (i.e. the number of cases in which the effect occurred) and a denominator (i.e. the size of the population exposed). Drug utilization studies play their role in identifying the denominator.

However rigid the criteria a drug must meet before it enters the market, the amount of information available on its merits and risks when it is launched will inevitably be limited. A drug can only finally prove itself in the field; only under the conditions of actual practice will the necessary experience be gained to build up, perhaps over many years, a full picture of the drug's properties, its risks, and the way it can be most safely and effectively used. Inevitably, that final process of evaluation will sometimes bring with it unpleasant surprises; the fact that rare but serious side effects occur after drugs have been approved for use has increasingly emphasized the need to assess drug safety, as well as effectiveness and appropriate use, at different levels of the health care system after marketing (1–5) (see also Chapter 2).

In the past three decades, a number of sensational therapeutic accidents have successively alarmed—and sometimes overwhelmed—health authorities, health researchers, health workers, and the public (6–9). Notable tragedies of varying character have included thalidomide-induced phocomelia, the chloramphenicol-triggered grey baby syndrome, the role of diethylstilbestrol in inducing vaginal cancer in the adolescent offspring of exposed pregnant women, clioquinol-induced subacute myelo-optic neuropathy, the induction of serious
effects on the skin and mucosa by practolol, and more recently benoxaprofen hepatotoxicity. Alongside these prominent disasters, numerous less prominent complications and accidents have occurred, many of which have arrested the careers of the drugs involved. Table 1 lists certain of the drugs that have been withdrawn from one or more countries after marketing, and some that have been subject to changes in formulation or product labelling, or about which warnings have been issued to prescribers. Concern has been expressed about the appropriateness of some of these regulatory actions (10), but one should be at least equally concerned about how to avoid in future the sort of problems that gave rise to them. In particular, increasing attention must focus on appropriate methods to assess drug safety in the post-marketing period.

Although, conceptually, postmarketing surveillance involves the study of both the efficacy (new indications or actual benefit) and safety of drugs after approval by the licensing authority, the term has most generally been used for long-term assessment in the field of the adverse effects of drug use. This chapter briefly reviews the major techniques used in the assessment of drug safety (and in particular the quantification of risk) in actual practice, as well as some methods for hypothesis testing that have been adopted from the field of epidemiology (11–15).

Signal generation

The postmarketing evaluation of drug safety serves two primary and equally important goals. First, it must provide a means of signal generation or the detection of new (i.e. previously unsuspected) and serious adverse drug reactions. Second, it must serve to quantify the risks involved so that the health authorities, health workers and drug manufacturers can take appropriate action, such as providing information or warnings to prescribers, changing the labelling of the product, changing its formulation, and sometimes even withdrawing it from the market.

In individual cases, it is virtually impossible to establish a causal relationship between drug exposure and a particular clinical outcome, whether beneficial or adverse. When evaluating benefit, one must consider that the outcome observed may be part of the natural course of the illness (remission or spontaneous cure) or the effect of other interventions (drugs or surgery). Similarly, an adverse event observed in a patient treated with a particular drug may be due variously to the disease for which the patient received the drug, a concomitant disease,
Table I. Some drugs that have been subjected to changes in regulatory status after marketing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse reaction</th>
<th>Changes in status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benoxaprofen</td>
<td>Hepatotoxicity</td>
<td>Withdrawal from one or more countries</td>
</tr>
<tr>
<td>Clioquinol</td>
<td>Subacute myelo-optic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Dipyrone</td>
<td>Agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Isoxicam</td>
<td>Immunological reactions</td>
<td></td>
</tr>
<tr>
<td>Indometacin</td>
<td>Gastrointestinal ulcers</td>
<td></td>
</tr>
<tr>
<td>Nomifensine</td>
<td>Immunological reactions</td>
<td></td>
</tr>
<tr>
<td>Phenformin</td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Practolol</td>
<td>Oculomucocutaneous peritoneal syndrome</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Phocomelia</td>
<td></td>
</tr>
<tr>
<td>Tienilic acid</td>
<td>Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Zimeldine</td>
<td>Guillain-Barré syndrome</td>
<td></td>
</tr>
<tr>
<td>Zomepirac</td>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>Aprindine</td>
<td>Agranulocytosis</td>
<td>Changes in labelling, product formulation or issuance of warnings to prescribers</td>
</tr>
<tr>
<td>Bismuth gallate</td>
<td>Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Pulmonary infiltrations, pleural effusions and thickening</td>
<td></td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>Vaginal cancer in offspring of exposed pregnant women</td>
<td></td>
</tr>
<tr>
<td>Emepronium bromide</td>
<td>Esophageal ulcers</td>
<td></td>
</tr>
<tr>
<td>Glafenine</td>
<td>Anaphylactic shock</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Eosinophilic lung reactions</td>
<td></td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>Psychic reactions, psychosis in children</td>
<td></td>
</tr>
</tbody>
</table>

Whenever an adverse event is observed during the course of treatment, the suspicion may arise that it is drug-induced. Although a number of algorithms have been developed to improve objectivity in the evaluation of individual case reports, cause–effect relationships often cannot be established with absolute certainty (16). The existence
of a series of similar cases may strengthen the suspicion that the adverse event is drug-related. Case reports and case series will, however, often simply provide evidence of an association between the drug and the adverse event and that hypothesis will still have to be confirmed. It becomes particularly important and urgent to seek confirmation when:

(a) the adverse event is serious;
(b) the adverse event is unusual (not expected from the pharmacological actions of the drug);
(c) there is any reason to believe that the adverse event is likely to occur frequently.

Hypothesis testing
The testing of a hypothesis requires the use of comparison groups (treatment/cases and controls) to determine whether there are differences in the variables of interest (risk factors, traits, characteristics, drug exposure or clinical condition). Statistical methods are used to assess whether the observed differences could have occurred by chance alone. Conclusions about the relationship between exposure to a drug and a clinical event are thus based on the acceptance or rejection of the null hypothesis, postulating that the comparison groups are no different with regard to either the drug exposure or the clinical event.

The major epidemiological research designs for hypothesis testing may be classified as experimental (randomized controlled clinical trial) or nonexperimental/observational (cohort and case-control). The experimental approach differs from the observational in that the researcher controls the assignment of the study participants to each study group, generally by random allocation.

Experimental studies in the postmarketing period have usually been concerned with evaluating the long-term wanted effects of drug treatment (17–22). On occasion, randomized controlled trials have been useful in detecting adverse effects and risks, such as the association between clofibrate and cholecystitis (23) or the increased risk of a second episode of myocardial infarction in patients receiving conjugated estrogens (24). But these experimental methods are in fact ill adapted to the assessment of safety, because of differences in conditions in routine clinical practice and because of various limitations regarding study size, duration and ethical principles. Hypothesis
testing in safety matters therefore has to rely largely on nonexperimental/observational designs such as cohort and case–control methods.

The cohort and case–control research designs take a different approach to the same problem (6). In a cohort study design, a cohort (i.e. a group of individuals with some common characteristic, such as drug exposure) is assembled and followed prospectively or retrospectively; a control group is assembled in which the single characteristic to be studied is lacking (i.e. subjects to whom no drug has been given). The two groups are then compared with regard to the incidence of relevant (adverse) clinical events.

In the case–control approach, the study group consists of cases presenting with a particular disease of interest, whereas the control group consists of individuals who do not have the disease. The two groups are compared with regard to the prevalence of drug exposure.

Case reports and case series are other observational research designs used in epidemiology. They are rarely useful for hypothesis testing, however, because of the lack of controlled comparison. Exceptionally, in some case reports, the subjects will serve as their own control, as when rechallenge (intentional or unintentional) with a particular exposure occurs. Comparison with other published series or historical controls is sometimes carried out when examining case series, in an attempt to provide control groups. This approach must be used with some caution, as conditions and characteristics in the two series compared may not be sufficiently similar or otherwise appropriate. With the exception of occasions where rechallenge occurs, individual case reports or case series of observed associations between a drug exposure and an adverse event should therefore be regarded as no more than sources of hypotheses that will require testing with cohort and/or case–control studies.

**Measuring Risks**

Once an association between drug exposure and adverse effect has been established, it becomes necessary to quantify risks, i.e. the probability that a given adverse event will occur as a result of drug treatment. Two common measures are used in drug epidemiology to estimate the likelihood that a given drug exposure is related to an observed adverse event: the relative risk and the attributable risk.

The relative risk is the ratio of the incidence of the problem in the study group to its incidence in the control group. It provides an
estimate of the strength of an association. A relative risk of 1.0 indicates that there is no association between the drug exposure and the disease of interest. A relative risk of greater than 1.0 means that the subjects in the study group are more likely to develop the disease than those in the control group. The greater the relative risk the stronger the strength of the association. A relative risk of less than 1.0 indicates that the subjects in the study group are less likely to develop the disease than those in the control group. In the latter case, the drug may actually be exerting a protective effect.

The attributable risk (sometimes termed the excess risk) is the absolute difference in incidence rates between the study subjects and controls when one is subtracted from the other. The attributable risk gives an indication of the impact of the drug-induced disease in the population at large. A complication that is generally benign but occurs frequently may have a greater effect on overall morbidity and/or mortality than a relatively serious complication that occurs only very infrequently (Table 2).

The individual prescriber will most want to know the relative risk associated with a particular drug exposure when treating a patient, whereas the health authorities will prefer to know the attributable risk in order to draw up an appropriate policy.

Both the relative risk and attributable risk can be calculated in cohort studies, as it is possible to determine the incidence of the adverse event concerned. In case–control studies, the odds ratio is calculated: among patients experiencing the adverse event, the ratio of those exposed to the drug to those not exposed to the drug. Normally, case–control studies do not provide estimates of attributable risk.

Table 2. Relative and attributable risks for a common and a rare drug-induced disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Relative risk</th>
<th>Attributable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding in the elderly</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>3</td>
<td>1000 per million users&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>Dipyrone</td>
<td>24</td>
<td>1 per million users</td>
</tr>
</tbody>
</table>

<sup>a</sup> Rough estimate based on calculations from published data.
Where all cases of the adverse event occurring in a defined geographical area have been included, however, the relative risk and attributable risk may both be calculated.

**Sample Size Requirements and Feasibility of Studies**

In the design and conduct of epidemiological research, the size of the study and control groups required will vary according to the size of the relative risk one wishes to detect and the incidence of the particular complication in the control group. Because of the size of most premarketing clinical trials, only relatively frequent risks will be detectable; a study of 500 subjects will be needed to detect a risk occurring once in 100 patients, and a study of 3000 subjects will be required to detect a 1:1000 risk.

Tables 3 and 4 present sample size calculations for cohort and case-control studies, respectively (6). For cohort studies, sample size requirements increase as the relative risk one wishes to detect decreases and as the incidence of outcome in the control group decreases. Similarly, for case-control studies, as the prevalence of drug use decreases and the relative risk one wishes to detect becomes smaller, the sample size must increase. Sample size requirements thus significantly influence the feasibility and cost of conducting postmarketing studies. Such data underline, once more, the inevitability of fully clarifying the safety of a drug only after it has come into use in the field, and once drug utilization studies have become a major instrument in studying it further.

**Development of Techniques for Postmarketing Surveillance**

Since the early 1960s, a number of operative strategies or techniques have been developed and used to monitor for adverse drug reactions (11-14,25,26). Spontaneous reporting systems led the way, but many others followed and evolution continues. The development and characteristics of the principal methods available today will be sketched in the sections that follow.

**Spontaneous adverse drug reaction reporting systems**

Initial work in postmarketing surveillance concentrated on developing national or regional systems to compile case reports of suspected
Table 3. Sample sizes for case-control studies

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>1/1000</th>
<th>1/100</th>
<th>5/100</th>
<th>10/100</th>
<th>25/100</th>
<th>50/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>23 596</td>
<td>2 398</td>
<td>516</td>
<td>283</td>
<td>152</td>
<td>137</td>
</tr>
<tr>
<td>2.5</td>
<td>12 239</td>
<td>1 247</td>
<td>272</td>
<td>151</td>
<td>85</td>
<td>81</td>
</tr>
<tr>
<td>3.0</td>
<td>7 870</td>
<td>804</td>
<td>177</td>
<td>100</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>5.0</td>
<td>2 954</td>
<td>305</td>
<td>70</td>
<td>41</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>7.5</td>
<td>1 587</td>
<td>165</td>
<td>39</td>
<td>24</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>10.0</td>
<td>1 072</td>
<td>113</td>
<td>28</td>
<td>18</td>
<td>14</td>
<td>19</td>
</tr>
</tbody>
</table>

a Calculations are based on a two-tailed alpha of 0.05, a beta of 0.2, and one control subject per diseased subject.

Source: Strom (6).

Table 4. Sample sizes for cohort studies

| Sample size required when the incidence of outcome in the control group is: |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                             | 1/50 000        | 1/10 000        | 1/5 000         | 1/1 000         | 1/500           | 1/100           |
| 2.0                         | 1 177 645       | 235 500         | 117 732         | 23 518          | 11 741          | 2 319           |
| 2.5                         | 610 627         | 122 108         | 61 043          | 12 191          | 6 084           | 1 199           |
| 3.0                         | 392 544         | 78 496          | 39 240          | 7 835           | 3 909           | 769             |
| 5.0                         | 147 201         | 29 432          | 14 711          | 2 935           | 1 463           | 285             |
| 7.5                         | 78 969          | 15 788          | 7 890           | 1 572           | 782             | 151             |
| 10.0                        | 53 304          | 10 656          | 5 324           | 1 060           | 527             | 100             |

a Calculations are based on a two-tailed alpha of 0.05, a beta of 0.2, and one control subject per exposed subject.

Source: Strom (6).

adverse drug reactions. Since then, much time has been devoted to developing the techniques to assess causality in individual reports (13).

Spontaneous adverse drug reaction reporting systems are based on the collection and analysis of case reports of suspected adverse drug reactions. In a spontaneous reporting system, specially designed cards or reporting forms are used by physicians to report suspected adverse drug reactions. The reports may be collected and analysed in national or regional centres.

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Spontaneous reporting systems have considerable merits and some limitations; their inability to provide quantified data is one of their weaker points. Of all the adverse events one might wish to see reported to such a system, only 1–5% actually seem to be reported, even to the most sensitive systems. Uncertainty about the proportion of instances of an adverse event that is actually reported makes any calculation of incidence hazardous; in the few cases where some estimate of incidence can be ventured, however (generally because the adverse effect is a serious one and the reporting rate is thus likely to be higher than usual), the calculation will depend heavily on the availability of reliable drug utilization data. The evaluation of lactic acidosis associated with the biguanides metformin and phenformin (27) and of the Guillain-Barré syndrome associated with the antidepressant zimeldine (28) are examples of this line of development.

Hospital-based intensive monitoring
The need to collect information concurrently on the extent of drug exposure and on adverse events, in order to make a proper quantification of risks, was a major consideration in the development of hospital-based intensive monitoring systems for adverse drug reactions (13). In this approach, trained health personnel monitor patients admitted to selected hospital wards by reviewing their clinical charts and conducting structured interviews of both patients and physicians. Such projects have proved useful for the study of acute and relatively common adverse drug reactions. Important limitations include, however, the inability to study adequately drugs that are used mainly in outpatient care, the short follow-up period (dictated by the limited length of hospital stays), and the small size of the patient populations. The strength of the approach clearly lies in the fact that the hospital can generally collect reliable information on the pattern of drug utilization within its walls; quantification is thus in principle possible.

Case–control studies and case–control surveillance
The essence of the case–control method has been outlined above. It will normally allow the calculation of an odds ratio; exceptionally, it may allow the estimate of both relative and attributable risk.

The case–control method is well suited to the study of rare complications or those with a long latency. Once such evidence emerges, drug utilization data can help determine the absolute occurrence of the complication in the population as a whole, bearing in mind any
evidence that certain subpopulations may be more affected than others. The method was developed for use in the drug field at the Boston University Department of Epidemiology, now the Slone Epidemiology Unit. The international agranulocytosis and aplastic anaemia study is an example of the case–control methodology, studying a number of drugs and rare but serious diseases (agranulocytosis, aplastic anaemia and thrombocytopenia) and involving centres in many countries (29–31).

**Cohort studies and cohort surveillance**

As noted above, the cohort method makes possible a calculation of relative and attributable risk. Coupled to drug utilization data on the drug in question (and the drugs that provide an alternative to it), the method is a formidable tool for determining the extent of drug risk in the population and for developing policies to keep it within reasonable bounds.

The cohort approach to routine data collection for signal generation and hypothesis testing has been applied in the development of prescription monitoring (13). This consists of seeking correlations between extensive records of prescribing patterns for particular drugs (obtained through a health insurance system) and the occurrence of adverse events. Developed as an independent national drug monitoring scheme, largely in response to the practolol tragedy, this method is employed at the University of Southampton’s Drug Surveillance Unit in the United Kingdom. The Department of Health of New Zealand has developed a variation of this approach as part of the drug regulatory authority’s activities, through the intensified reporting of adverse events (13).

**Medical record linkage and computer databases**

The availability of computerized pharmacy and medical records in certain health organizations/settings has facilitated the development of medical record linkage for postmarketing surveillance (32–35).

Medical record linkage is essentially a method of data collection, linking available medical and pharmaceutical records on a patient-specific basis. This is currently achieved through computer technology, and a number of variants are available:

(a) the computerized collection and analysis of both medical and drug prescription records for individuals covered under a particular health care system;
the linkage of hospital discharge data and prescriptions for specific individuals covered by a health plan;

the linkage of medical with pharmacy billing claims.

The method allows for a highly objective study of long-term and late complications, linking well documented complication data and equally well documented use of drugs at the individual level, in a manner that no other method can achieve. As a by-product of administrative processes, it can be relatively inexpensive and it proves useful for both signal generation and hypothesis testing. On the other hand, the quality and extent of drug exposure and diagnostic information must be validated (for example, through access to primary records); information on extraneous variables, which could confound the correlation, is usually incomplete; and a one-to-one relationship rarely exists between the drug dispensed and the stated indication for drug treatment.

Currently, this ambitious approach to data collection for postmarketing surveillance appears to be feasible only in countries with highly organized health care systems. Even there, however, because of the variable quality of the computerized data, it is imperative to have access to primary medical records, prescribers, and/or patients.

**Comparative Yield of the Various Methods**

Two examples may illustrate the differences in the results obtained with the principal methods used to evaluate drug safety and quantify risk. The first relates to the evaluation of associations between drugs and rare but grave diseases, such as agranulocytosis and aplastic anaemia. The other example relates to links between drugs and more frequent problems, such as gastrointestinal disorders and peptic ulcer complications.

**Drug-induced agranulocytosis and aplastic anaemia**

Published risk estimates for agranulocytosis induced by non-narcotic analgesic drugs were recently reviewed by Laporte & Carné (36); agranulocytosis and aplastic anaemia are the leading causes of drug-induced death, as shown by data reported to the Swedish Adverse Drug Reaction Committee in 1966–1975. A causal relationship between these rare but severe diseases and the pyrazolones has been established,
on the basis of case reports and case series, including positive rechallenges (37).

Estimates of risk for agranulocytosis with these drugs vary from 1 in 116 to 1 in 466,000 exposures in a number of studies. These estimates have, however, been obtained in studies that are biased either by non-random selection of cases or the lack of a proper control group (36). The use of a prospective control group (i.e. the construction of a cohort study) is impossible because the blood dyscrasias are very rare diseases (with an estimated incidence of 2–6 per million); the sample size required would be several million subjects. Results from the international study of agranulocytosis and aplastic anaemia indicate relative risks for agranulocytosis lying between 0.8 and 23.7, and an excess risk of 1.1 per million for the non-narcotic analgesic dipyrone (30).

The analysis of these estimates in relation to available drug sales data by Laporte & Carné (36) suggests that the risk estimates obtained in the international study are more compatible with the lower estimates of the incidence of agranulocytosis (between 2 and 6 per million).

Peptic ulcer complications and nonsteroidal anti-inflammatory drugs

A review by Langman of peptic ulcer complications and the use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAID) (38) provides a useful illustration of the relationship among the main observational methods for assessing adverse drug reactions of this type. Data from voluntary reports on adverse reactions show that drug-induced peptic ulcer and related complications constituted a quarter of all reports submitted to a voluntary reporting system by physicians in the United Kingdom, with 3500 such reports in a year. The figure cannot, however, be related usefully to available prescribing data for NSAID since the reporting rate is not known, and since various factors can bias the distribution of reports among the various marketed compounds. Some drugs have been marketed for longer periods than others (for example, indometacin longer than piroxicam) and more adverse reaction reports tend to be submitted for newer agents. Again, as a result of promotional claims, a particular drug thought to be safer than others may be used precisely in those patients likely to be at high risk (such as elderly or dyspeptic patients).

For such reasons, both the widely accepted hypothesis that NSAID are associated with an increased risk of peptic ulcer complications and
the actual incidence of the complication in this connection were investigated using both the cohort and case–control approaches.

The cohort study quoted by Langman (38) involved five groups of patients (a total of 62 000) taking benoxaprofen, fenbufen, zomepirac, piroxicam or osmotically-released indometacin. The results indicated that peptic ulcer complications accounted for between 2 and 6 events per 1000 patient-years of drug exposure. No noteworthy differences were detected among the drugs. No differences were observed when the event rates were compared in the patient groups receiving one of these drugs and those not doing so; however, a patient not receiving one of the drugs may have been taking another NSAID, such as acetylsalicylic acid, naproxen or plain indometacin.

The case–control study compared 230 patients over 60 years of age with bleeding gastric or duodenal ulcers with two control groups (acute medical ward patients and community controls). The results suggested a relative risk of 2.7 for gastrointestinal complications associated with the use of NSAID in these patients (39). The data were insufficient to determine whether any of the drugs were particularly risky.

Finally, Langman used available data on drug utilization (based on prescriptions) to estimate the event rate likely to be encountered by the individual prescriber. It emerged that although several thousand cases of gastrointestinal bleeding and perforation may be attributed to NSAID every year in the United Kingdom, a general practitioner writing a thousand prescriptions a year for these drugs is still only likely to see one case of NSAID-associated gastrointestinal bleeding or perforation every five years (38)!

The studies summarized above are only part of the total picture; many other attempts have been made to quantify the gastrointestinal risks of NSAID (40–44). That the findings continue to show marked discrepancies may be attributable to a series of biases (such as marketing differences, prescribed dosages or age-related selection of study individuals) or to the sample sizes employed.

A Comprehensive Approach to the Study of Drug Effects in the Postmarketing Period

As previously pointed out – and as is evident from the above examples – no single method will cover all the needs of postmarketing surveillance; each method has its own advantages and its own limitations. In the current state of the art, evaluating the effects of drug use (beneficial
and adverse) seems to require a comprehensive approach that combines the various available methods. Such an approach will need to include descriptive surveys of patterns of drug utilization, means of identifying possible new and rare adverse drug effects (spontaneous reporting, and case–control and cohort surveillance) and instruments for testing hypotheses (including a network of centres to conduct further cohort and case–control studies where they are required).

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The social aspects of drug use

F.M. Haaijer-Ruskamp & E. Hemminki

Increased awareness of the problems associated with drug use, such as over- or underutilization and inappropriate use based on available clinical pharmacological knowledge, emphasizes the need to ensure that medicines are properly and safely employed. In this context, it is important to understand why and how drugs are given and taken. Although this may seem self-evident, it is an area full of misconceptions.

Drug use is determined by a great many factors. To understand it, one must make use of the insights of pharmacology, epidemiology and the social sciences (Fig. 1). Clinical pharmacology is needed to investigate the safety and efficacy of drugs. Epidemiology helps one to understand the extent and pattern of drug use, and what such drug use actually contributes to health. More recently it has been acknowledged that a complete assessment of drug use should also take the social aspects into account; the social sciences can explain how the perceptions of individuals as well as the social and cultural environment can affect drug use.

Drug use, as part of the process of medical care, requires the people who give and take drugs to make various types of decision. At all points, they are affected by their varied cultural values (not necessarily limited to health and illness), by their social networks and by psycho-social factors. Sometimes the influence is diffused throughout the whole process, sometimes it is specific to particular phases or participants. The process, moreover, takes place in a specific organizational setting provided by the health care system, which has its own influence on events by determining the availability of medical care services as well as drugs.

The social or cultural setting in which a drug is given or taken may also influence people's response to the drug, as is illustrated by the
Fig. 1. Drug use in society: the need for a multidisciplinary approach

placebo effect. The placebo effect is generally culture-bound, since it depends on how people view the world; it can be modified by factors such as the social setting in which the treatment is administered, and by the expectations of both the drug giver and the drug taker (2,3).

Finally, alongside their pharmacological effects, drugs have social, cultural and psychological effects: drug use may affect the way people view themselves, their motivation to solve their problems and, in general, their quality of life.

In short, the social aspects of drug use embrace a wide range of issues. This chapter considers the framework behind the various social aspects of drug use and outlines some general methodological considerations of importance for this type of research. The emphasis is on the major explanatory perspectives as they have emerged. First, drug use is discussed at the micro-level as part of the medical care process, focusing on self-medication, on the physician’s prescribing behaviour and on compliance and non-compliance. Then the chapter turns to the macro-level and describes the effect of the health care system and
cultural differences on drug use. The theoretical perspective determines the methods to be used. Therefore the different perspectives are described first, followed by some methodological considerations. Because of the great number of studies, only comprehensive reviews and selected empirical reports have been referred to. Many earlier reviews and comprehensive studies have proved especially helpful.

Drug Use as Part of the Medical Care Process

The different steps in the medical care process are summarized in Fig. 2.

Self-medication
The first step in the drug use process involves the decision of what to do in the event of perceived illness. Of the very many symptoms an individual experiences, only a small proportion (estimates vary from 10–30%) are brought to the attention of a physician. Many symptoms will simply be tolerated as minor inconveniences and some will pass almost unnoticed. Where there is a response it usually takes the form of self-medication as a means of “normalizing” the situation. Little research has so far been carried out on the social and psychological aspects of self-medication, but some influences can be detected. Self-medication is the solution most likely to be adopted when relief is wanted but the perceived severity of the symptom and its anticipated duration give the patient no cause for concern; it is thus employed most commonly for self-limiting diseases that involve only minor discomfort or are perceived as non-serious. Professional care is sought when the results do not meet the user’s expectations (4). Self-medication can also be the alternative when professional care is not available or affordable.

Many studies addressing the relationship between sociodemographic variables and self-medication show that self-medication is most common among women, older people and people of the higher socioeconomic classes. These factors are related to the amount of perceived ill health, however, which varies between these groups. Recent research has focused more on the psychological and social forces that underlie the decision to self-medicate, but no strong predictor has been found.

From this point of view, self-medication is an aspect of illness behaviour, the way people perceive and react to symptoms. Illness behaviour is affected, for example, by the social network (notably friends and family). The social network shapes one’s attitude to health;
Fig. 2. Drug use as part of the medical care process

Illness → Professional care → Diagnosis → Therapy → Compliance → Drug use

Revisits

Drug therapy

Individual social and psychological factors
- Self-care
- Self-medication
- Patient's expectations
- Patient's ability to cope

Health care system
- Availability of medical care
- Availability and quality of drugs

Cultural values and beliefs about health and illness

Physician–patient communication
- Physician's knowledge, attitudes and norms
- Patient's health beliefs, attitudes and norms
- Social and psychological functions of drug use

Patient's expectations
- Physician–patient communication
- Diagnostic process
- Physician's attitudes
- Patient's attitudes

Patient's ability to cope
- Physician–patient communication
- Physician's attitudes

Physician's attitudes
- Availability and quality of drugs
- Availability of medical care
it provides knowledge and skills related to health and it provides social support and coping ability (5,6). One important psychosocial factor is the benefit expected from alternative actions. This expectation is often based on past experience; people may, for example, self-medicate because they expect or know from experience that professional care can do little for their illness, as in the case of the common cold. In other cases, they may choose self-medication primarily because it has helped them in the past (7).

Prescribing behaviour
Much research on the social aspects of the use of prescribed drugs has focused on the factors that influence the prescribing behaviour of physicians; this is understandable because the physician is the gatekeeper of formal medical care and to a large extent determines drug use (8–11). A large part of that research has set out to document variations in rates and costs of prescribing among individuals and populations, and the extent to which these are influenced by selected individual factors, particularly sources of information and physician characteristics. Although such work has been helpful in identifying problem areas, it has tended to be largely descriptive, raising more questions than it answers about the causes of the phenomena.

Some models have, however, provided a more systematic conceptual approach. Hemminki (10,11) distinguishes between factors that affect prescribing at the macro-level (so-called conditioning factors) and factors that influence individual physicians. The main conditioning factors are (11):

(a) the traditions and education of the population, which may mould both the expectations of the patients and the views of the physicians;

(b) medical teaching and professional thinking, which define the concepts of health and illness and thus determine the use of physician services;

(c) the level and distribution of wealth in a country and the ideology and power of the state, since these can affect the organization, regulation and availability (geographic and financial) of both professional care and drug supply;

(d) the power and vitality of the pharmaceuticals industry.
The way these conditioning factors may act on the factors influencing individual physicians varies from time to time and from country to country. Their overall effect is clearly important, but there is still much to learn about their effects on individual prescribing.

Fig. 3 shows a model of the factors that influence individual physicians. The three major individual factors in the model that penetrate to the micro-level to influence individual physicians are:

(a) the demands and expectations of pressure groups and society

(b) the influence of the pharmaceutical industry and research results

(c) the control measures and regulations imposed by the health authorities.

These major forces naturally influence the individual mainly through intermediaries. Some of them act primarily through pre- and postgraduate education, and professional and commercial information to physicians. Colleagues, consultants and other health professionals are depicted as another source of influence, and they in turn are also influenced by the above-mentioned factors. The individual patient's personal characteristics, demands and expectations are direct influences but are again naturally moulded by society. The effect of all factors on what is actually prescribed is mediated by the physician's personal characteristics, working conditions and therapeutic resources.

The literature demonstrates the impact of most of these individual factors on prescribing, especially the effect of sources of information. Clearest perhaps is the impact of the pharmaceuticals industry, which has several channels of influence: it exerts pressure directly by its marketing mechanisms, its travelling drug representatives, the provision of journals and other printed material, drug samples, drug discounts, exhibitions and patient aids, and a variety of public relations activities, such as excursions, parties and gifts. Several studies have shown that an insufficiently critical attitude towards these activities of the pharmaceuticals industry is associated with poor prescribing. The impact of the indirect channels is less well studied, but may be equally important. Indirect channels are financial support and other help (such as know-how) for medical research, the financial support of medical journals and associations, the finance and organization of medical education (especially postgraduate education), the
Fig. 3. A model of the factors that affect individual physicians

Control and regulations from health authorities, health insurance systems, medicines committees

Research results

Pharmaceuticals industry

Demands and expectations of pressure groups and society at large

Consultants and colleagues

Advertising (information)

Undergraduate and postgraduate education

Medical and scientific journals

Patient's personal characteristics

Patient's demands and expectations

Tradition and role of physician's profession

Other health professionals

Physician's personal characteristics

Physician's working conditions and therapeutic resources

Prescription

Other forms of therapy

Outcome of therapy

Feedback

Feedback

Feedback

Source: Hemminki (11).
production of educational material and the maintenance of a position in society through close relations with leading physicians, health authorities and politicians.

These examples of the influence exerted by industry show how many different but interrelated processes need to be examined if one is to understand how even a single source of influence, such as the pharmaceuticals industry, exerts its effects. There is also still a considerable gap in the knowledge of how the individual factors in Hemminki’s model interact and of their relative importance. Haaijer-Ruskamp (12) used Hemminki’s model in a study of prescribing by general practitioners in a representative region of the Netherlands, thus keeping the effect of conditioning factors and the three major individual factors constant. Taking the relationships between these various factors of influence into account, the model explained 35–43% of the variations between the general practitioners as regards their overall prescribing behaviour (such as rates, cost or quality). It also explained 25–57% of the variations in the prescribing rates for different groups of drugs. Thus, the proportion of variation that can be explained varies, and much remains unexplained. This suggests that, while Hemminki’s model is useful in studying the influence of general factors, it does not provide insight into more subtle mechanisms.

A problem with trying to explain inter-physician variation is that the phenomenon to be explained is the end product of a number of decisions; the differences in drug prescriptions on an aggregate level (Fig. 2) reflect differences in the frequency with which patients consult their physician and differences in the diagnostic process. Any answer obtained therefore soon leads to a new question; one runs constantly into the problem of explaining the results that have been found.

Another major shortcoming is that the model does not include the cognitive processes of decision-making or the social and psychological functions of prescribing. A promising approach to understanding the cognitive process of prescription decision-making is based on the expectancy-value theory, derived from social learning theories. Basically this means that prescribing is the result of a rational decision, weighing the probabilities of benefits against the risks of the drug therapy. Knapp & Oeltjen (13) considered prescribing decisions to be based on subjective expectations about benefit (efficacy) and risks (side effects), the actual degrees of benefit and risk that may arise in specific situations, and other factors relating to the severity of the illness and physician characteristics. Their results indicate that the
physician’s specialty and the severity of the illness were highly relevant for the type of drug chosen, but were unrelated to prescribing rates.

A limitation of Knapp & Oeltjen’s study is that the appraisal of benefits and risks was defined only in terms of pharmacological effects. Segal & Hepler (14) extended the theory to include other aspects of the drugs and the opinions of colleagues. They based their research on a more detailed expectancy–value theory developed by Fishbein & Ajzen (15). In studying the process of drug choice, Denig et al. (16) went further and integrated the role of opinions held in the professional environment (by colleagues, specialists and pharmacists), prior experience with the drug, and perceived patient demand (Fig. 4).

All these aspects appear to be important elements in the overall appraisal of a drug, and it is encouraging that, in the studies both of Segal & Hepter and Denig et al., the actual drug choice could be predicted correctly. Understanding the process of drug choice is particularly important if one is to improve prescribing. For example, Denig et al. found that knowledge about pharmacological effects and side effects determines drug choice only in part; the opinions held in the professional environment are just as important. This implies that educational programmes for groups may be more effective than individual approaches.

The elements not included in the above-mentioned models are the social and psychological functions (as opposed to the merely pharmacological) fulfilled by prescribing and drug use. Several authors (17–21) have shown that prescribing may have such functions for both the prescriber and the patient. For the prescriber, a prescription can symbolize willingness to help, or it may function as visible evidence of professional ability; it can also serve as a cue to end the consultation. Prescribers may deviate from known professional standards in order not to lose patients. For the patient, a prescription may symbolize the physician’s interest in his or her welfare, confirm that he or she was right to consult the physician or justify his or her assuming the sick role. Svarstad (21) suggests four propositions that may deepen the understanding of the functions of prescribed drugs.

1. Drug giving and taking may serve symbolic or expressive functions (as in the above examples).

2. Drug giving and taking may serve manifest (recognized, intended) as well as latent (unrecognized, unintended) functions. As an
Fig. 4. A drug choice model

- Personal experience
- Value of personal experience
- Expectations about treatment outcomes
- Value of these outcomes
  - such as: efficacy, side effects, compliance, costs
- Expectations about opinions of social environment
  - such as: colleagues, specialists, pharmacists, patients
- Motivation to comply with environment

Weighed experience with prescribing of drug X

Attitude towards prescribing of drug X

Subjective norm towards prescribing of drug X

Moderating factors
  - such as: incidence of disease, availability of drug

Drug choice

Prescribing

Source: Denig et al. (16).
example of a latent function, she notes that tranquillizers may be used in nursing homes to reduce the workload of the nursing personnel. Comaroff (18) suggests that a latent function of placebo therapy is to cope with ambiguities in the clinical situation.

3. One drug can serve different functions for different people or for the same people in different situations or at different times. Especially relevant in this context is the distinction between initial use and regular or continuous use. A classical study by Balint (22) shows that continuous repeat prescribing may function as a “solution” in an unsatisfactory physician–patient relationship.

4. Different drugs can serve the same function. For example, several quite different types of drug may be used to cope with anxiety.

Only a few studies so far have included these social and psychological functions, probably because of the difficulties of handling them. Unless one understands these mechanisms, however, one’s efforts to ensure safe and effective drug use may fail.

A completely different approach is to understand prescribing as a part of the physician–patient interaction during the consultation. Raynes (23) found indications that some general practitioners develop particular routine approaches to the patient, which they use regardless of his or her presenting symptoms. Heath (24) used an ethnographic approach to illustrate how physicians and patients interact during the actual prescription writing – not only verbally but also by non-verbal cues, such as bodily shifts, pauses and breaks. As Christensen & Bush (9) note, this approach is particularly useful in understanding such matters as physician dominance, patient satisfaction and patient comprehension.

Raynes (23) draws attention to the function of a prescription in the diagnostic process, which she views as an empirical evaluation process. A physician may try out a drug and infer the diagnosis from the patient’s reaction to it. In this way, uncertainty, which is inherent in primary health care, may be managed. The recall visit can thus be used to evaluate the patient’s problem.

**Patient Compliance and Non-compliance**

The central issue addressed by studies of actual drug use by the patient is non-compliance. Many patients do not use prescribed drugs as instructed by their physician. Non-compliance has become an important issue in both medical and social scientific research and it is also
discussed in Chapter 9. Analysing and studying the concept itself is problematic all the same (25).

Some reasons for non-compliance are associated with the drug therapy itself; non-compliance becomes more pronounced where the prescribed treatment is complex (26), where treatment is prolonged (27) or where there are troublesome side effects (28). From the social sciences, three explanatory theories have emerged to deepen the understanding of the behavioural determinants of compliance and non-compliance.

The first of these theories places the source of non-compliance in the physician–patient interaction or communication. Compliance will be better where the instructions given to the patient are explicit and understandable (21, 29, 30). Patient satisfaction is relevant; a patient who is satisfied will be more compliant. Other researchers have pointed to the relevance of the physician’s communication style (29–32), stressing the importance of motivating the patient besides providing him or her with information.

The second theory, based on an expectancy–value theory (the health belief model), has increased the understanding of the role of patient beliefs in compliance (33–36). Like the physician who is making a decision on prescribing, the patient who has received a drug goes through a rational decision process, based on his or her knowledge and expectations. The patient’s beliefs about his or her own illness and its severity, the expected benefits of the drugs and the costs of treatment were found to be important predictors of compliance, as were patient perceptions about the views of his or her immediate circle.

More recently, both these theories have been challenged as being too medically centred, with non-compliance being viewed primarily as deviant or disobedient behaviour (37). Moreover, the physician–patient interaction perspective assumes that the physician is central to compliance. The expectancy–value theory includes the patient’s behaviour as the result of rational decisions based on health beliefs, but it ignores other aspects of his or her experience. After the consultation, after all, the matter may be discussed and evaluated with family and friends; the outcome of this evaluation may well be decisive for the patient’s actual behaviour. It has also been pointed out that, to the patient, medication is only a small part of everyday life, even when it is being taken for chronic illness.

In the third theory, the overall significance of the drug to the patient is the central issue. Although there are only a few studies and much
of the evidence remains inconclusive, this theory has produced some interesting results. For example, in a study of the significance of anti-epileptic medication for the user, Conrad (37) found that the reason why people do take these drugs is instrumental: i.e. drug-taking can help people lead a "normal" life or it can reduce worry. This instrumental perspective is not limited to the use of anti-epileptics, but has been noted with other groups as well (38, 39).

The drug may also be viewed as an indicator of the degree of the disorder, a change in medication implying for the patient a change in the severity of the disorder. Moreover, in general, people seem to dislike taking medication, even if they do take it. In this context, non-compliance becomes more understandable. In fact, it appears that a large part of non-compliance is a form of self-regulation by the patient. Conrad found four major reasons for self-regulation (in the sense of reducing or stopping the medication) by epileptic patients. It can be:

(a) a way of evaluating the current state of the disease;
(b) a desire to avoid drug-dependence and, in general, to assert control over the disease;
(c) an attempt to overcome the stigma of chronic invalidity that chronic treatment is felt to confer; or
(d) an attempt to prevent the disease interfering with daily life.

Other studies support Conrad's findings applying the same perspective to other drug groups (40,41).

The theories described here are not mutually exclusive; indeed an integration of the physician's and the patient's perspective would seem to strengthen the understanding of the phenomenon of non-compliance and to help find ways to deal with it. One should accept that non-compliance or self-regulation is not deviant behaviour, but may be a very appropriate way of handling medication. In fact, it may often point to the need to consider anew whether drug therapy is actually required.

**The Influence of the Health Care System**

As pointed out in the introduction to this chapter, the health care system – or the organization of health care – is of interest in understanding drug use because it determines the availability and
Fig. 5. The health care system and drug use

As part of the planning and organization of health services, the health authorities provide independent information on drugs.

The pharmaceutical industry develops and produces drugs.

The health authorities regulate drugs.

The pharmaceuticals industry markets drugs and provides information on them.

Wholesale companies distribute drugs.

Physicians prescribe drugs.

Pharmacists dispense drugs.

The population uses drugs.

accessibility of medical care and drugs (Fig. 5). Health care systems vary widely from country to country because they are embedded in the different history and social, cultural and political values of the countries. Thus, for example, the principle of equal access to medical care is associated with a more general emphasis on social equality and with a sociopolitical structure that more readily accepts governmental control.
All the same, the effects of the health care system in the field of drug use have rarely been studied. Existing research focuses on drug regulation (i.e. licensing and registration) and control by the health authorities, on the pharmaceutical industry and on the role of the pharmacist. More recently attention has been given to the impact of reimbursement systems (discussed in Chapter 7, which focuses on the economic aspects of drug use).

Some form of regulation exists in every country, but its scope and content vary widely. In some countries, the task of regulation is primarily to ensure that only efficacious and safe medicines are allowed on the market; in others, regulation also covers the manufacturing process and distribution. The study by Dukes (42) provides an extensive discussion of the effects of regulation. One question that has been studied is the effect of regulation on the pharmaceuticals industry, mainly in the United States because of the so-called regulatory controversy. It has been claimed that excessive regulation delays the availability of useful new drugs and impedes research and thus innovation. These claims have not been proved; the results of many of the studies have been criticized for their unclear definitions and lack of valid data. Moreover, major therapeutic advances do not appear to have been retarded outside the United States. Industrial research is clearly affected by regulatory demands and licensing requirements, however, since these largely determine the types of study that must be performed to gain approval.

Dukes lists seven types of study that can and should be performed if the effects of regulation are to be assessed:

(a) an international comparison of two or more regulatory systems that differ in some clear respect, looking at their efficiency and the effects of the differences on drug use;

(b) studies of the validity and effects of specific measures and policies that have been contested by the pharmaceuticals industry and/or the medical profession;

(c) studies of the national effects of a national regulatory system on the pharmaceutical industry, in a country where the industry is substantial and innovative and has a large home market;

(d) studies of the way a particular drug has been handled by the regulators;
(e) studies of the effects of restrictive measures imposed in only one country on the incidence of drug-induced injury;

(f) studies of the influence of regulation on drug use in medical practice;

(g) studies of the impact of regulations on the quality of clinical trials.

The overall impressions from the results of the (limited) research carried out so far are that, in general, drug regulatory agencies are essential in defending the public interest with regard to the efficacy and safety of the drugs on the market (42,43). In some respects, however, regulatory practice differs substantially between countries, such as with regard to the therapeutic categories of drug that can be sold without prescription; the consumption patterns of these products are obviously influenced by these differences (44). The details of regulatory decisions also differ, notably with regard to approved indications, contraindications and warnings, although in these respects the repercussions of regulatory decisions on actual drug use in medical practice seem to be limited. No studies in the industrialized world have investigated the extent to which the total number of drugs on the market affects the quality and quantity of prescribing. Many assume that a smaller range would promote more appropriate prescribing, because it would be easier for physicians to be familiar with the whole range, but the concept of a limited range is violently contested.

Both the health authorities and the pharmaceuticals industry, however, have a much broader impact on actual drug use than that exerted by the number and quality of the drugs on the market. Health authorities can influence drug use by the regulation of trade, deciding who can produce and who can sell. They also affect drug use indirectly through the planning and organization of health services, including the availability of medical care (or the number of physicians), the number of pharmacies and specific prescribing regulations (which drugs are prescription-free and limitations on who can prescribe and in what quantity). In some countries, health authorities have direct control over clinical trials of unregistered drugs. Finally, health authorities play an influential role by providing independent information, by regulating commercial information and by setting requirements for postgraduate training. The impact of these aspects has been little studied. Bush & Osterweis (45) included the availability of
professional care as an enabling factor in their model to explain drug use. They found that a limited availability of professional care leads, to some extent, to the use of self-medication as a substitute. A more recent study supports this view in the case of poor access to formal medical care (46). In the context of complete insurance cover, however, this study found self-medication to be an adjunct to formal medical care rather than a substitute. One reason for this is that, during consultations, physicians not infrequently suggest that the patient might use over-the-counter medication.

The pharmaceuticals industry has a major impact because of its dominance in the dissemination of information. The scope of the commercial information flow has been studied by assessing the amount of money spent on advertising and the industry's travelling sales representatives (47, 48), or by cataloguing the amount of information received by physicians (49). Others have examined the quality and type of information provided by the industry (49–51). The information in commercial drug compendia is so voluminous and detailed that physicians relying on them may be led astray. Some of these compendia comprise only texts approved by the regulatory authorities, but others do not; in the latter, indications for use have been found to be excessively broad and listings of adverse reactions incomplete, and, since information is not presented in the same way for all drugs, a logical choice may be impeded. Moreover, the travelling representatives of drug firms are prone to omit the negative aspects of drugs in the information they provide. Finally, the use of the double name system, with both trade and generic names in use, leads to confusion (51).

Silverman (52) compared the promotional activities for identical products in a range of countries with the nature of regulation in those countries; he found that stricter regulations result in more truthful commercial information for the prescribers. The effect of commercial information on actual drug use has been studied mainly in terms of its effect on prescribing by physicians. Most such studies point to a negative effect: commercial information leads to higher prescribing rates and higher costs, a greater degree of inappropriate prescribing and inadequate knowledge (see, for example, Avorn et al. (53), but this view is contested by Smith (54)). More recently, attention has been devoted to the influence of direct advertising to the general public (55), a phenomenon traditionally limited to over-the-counter remedies but now becoming apparent for some prescription products as well.
Traditionally, the pharmacist’s primary responsibility has been the correct dispensing of drugs and the pharmaceutical quality of the drugs dispensed (56). In the last decade, the role of the pharmacist has changed. From a sociological point of view, this can be described as a process of professionalization, reflecting an attempt to become more involved in drug use (57). The loss of the traditional function of compounding drugs in the pharmacy had, after all, reduced the pharmacist to a retail supplier. The recognition of the need to improve drug therapy, however, gave pharmacists the opportunity to exchange part of their old role for a new involvement in drug use, based on their technical competence in the field and a willingness to adapt.

Their new role involves advising the physician about drug therapy, counselling patients about drugs and monitoring drug use (58, 59). Up to now, these activities have not developed to the same degree in all western countries. The pharmacist’s role in information is developing most markedly in the United States, Canada and some northern European countries. In the United States, experiments have been undertaken allowing the pharmacist to prescribe for some specified disorders, a role traditionally accorded only to the physician; in most states of the United States, the pharmacist is allowed to substitute generic drugs for brand name products (60). In the Netherlands, emphasis has been laid on the pharmacist’s role in monitoring drug use and, to a lesser degree, in informing the prescriber (61). Another issue is the effect of including the pharmacist in primary health care group practices, where he or she may be actively involved in drug choice and use. On the other hand, some recent developments in the Netherlands and the United Kingdom point to the increasing commercialization of health care, including pharmacies (62, 63); this must not threaten the concept of the pharmacist as a health professional acting in the patient’s interest. If, as is still the case in most countries, pharmacists continue to be remunerated primarily or exclusively on the basis of the drugs they sell, their involvement in the drug use process will be seriously hampered (64, 65). What is needed now is a better understanding of the potential of the pharmacist to play a broader role in the health care system, and the means to realize that potential.

The Cultural Perspective

Although the relevance of the cultural setting for drug use is widely recognized, few if any systematic studies exist in the industrialized
world. Cultural factors pervade all aspects of drug use, which is embedded in a matrix of social values and expectations. The cultural setting determines how society views drug use: its social acceptability and its social significance.

In this context, the concept of medicalization is pertinent, i.e. defining an increasing number of human experiences as medical problems. While, on the one hand drug use has increased as a consequence of medicalization (as is well illustrated by the use of psychotropic drugs), the development and production of effective drugs have also contributed to the process of medicalization itself (66).

The relevance of the cultural perspective is highlighted in anthropological studies of drug use in less developed countries (67, 68). Some of these studies illustrate how cultural definitions of health and illness lead to a reclassification or reinterpretation of western drugs (69–71). One should not assume, however, that in western countries no corresponding differences in concepts of health and illness exist. Zola (72, 73) showed, for example, how the cultural background in the United States affects people’s perception and presentation of their symptoms and their ensuing drug use. Sachs (74) describes what happens when two cultures meet, in this case Turkish women in the Swedish health care system. The Turkish women appear to believe that all illness can be cured, provided one gets the right medicines. In some cases, they regard traditional medicine as the best solution, in others – especially when they believe that microorganisms are involved – they prefer the Swedish physician and antibiotics. Cultural views of conditions that require treatment differ. Thus what is regarded as necessary treatment in one culture may be seen as amounting almost to malpractice in another. Germans, for example, regard low blood pressure as a condition to be treated by drugs, while physicians in the Anglo-Saxon world regard such treatment as over-medication (75).

Studies discussed earlier in this chapter, which delineate the patient’s perspective of drug use (37–39), emphasize that drugs are used as a means to lead a normal life, in other words, to meet social expectations, whether at work or within the family. Obviously, these expectations are determined to an important extent by the cultural setting.

Failure to understand the local/cultural perspective of medication will lead to inadequate communication about drug use; people, after all, base their actions on what they believe in. Cultural influences also clearly underlie the very different ways in which society determines the responsibility for drug-induced illness. Dukes & Swartz (76)
discuss the various approaches taken in different countries and discern an emergent global scheme according to which responsibility (legal, disciplinary or moral) is increasingly being apportioned.

Some Methodological Considerations

The variety of the issues, the complexity of the problem and the interdependence of influencing factors call for a diversity of conceptual approaches, involving many different methods. The merits of all the techniques that have been proposed or applied cannot be discussed here, but some general observations can be made.

Basically, two major methodological schools of thought can be distinguished: qualitative (sometimes also called anthropological) research and the quantitative (often biomedical) approach. Although there has been (and sometimes still is) a major controversy between the two, here they are viewed as complementary.

Qualitative research

Qualitative research may comprise interactionism or anthropological research. It emphasizes the individual perspective; extensive contact with the people involved is therefore a prerequisite. With regard to drug use, it has been called the bottom-up perspective (67, 77). Where there is a conflict between the anthropological and the biomedical approach, it may be attributable to the emphasis on the individual’s perception in the former. What might be perceived as irrational from a biomedical point of view may well be the most meaningful and therefore rational for the individuals involved. Participant observation (sometimes direct, sometimes more unobtrusive) and in-depth, open-ended interviewing are the traditional and most frequently used methods of data collection (77). More recently, historical sources have gained increasing attention because of a growing interest in evolutionary developments. This type of approach has, for example, shown how differing conceptions of disease and drugs lead to differences in drug development, as illustrated by the contrasting place of anti-anginal drugs in Anglo-Saxon and German medicine (78).

Qualitative analysis is especially suitable for studying the meaning of drug use, such as the social, cultural and psychological functions of prescribing or drug taking. It is also an excellent means of understanding the social and behavioural process, by tracing the links between the different stages of the drug use process. As such it can have an important hypothesis-generating function, such as when measurable
factors appear to play a role. Because of the complexity of the drug use process, the value of qualitative analysis is likely to be greatest when it takes place in well defined situations, controlling for confusing effects (in the first place, medical factors) by using homogeneous groups. To increase the reliability and general applicability of the results, one may need to study a variety of such homogeneous groups, changing one factor at a time.

Qualitative analysis is not appropriate when the purpose of the study is to analyse the extent to which one factor influences another; for that purpose, one needs to use quantitative methods.

**Quantitative analysis**
Quantitative analysis may comprise purely descriptive or explanatory studies. Central issues are the ability to measure phenomena exactly and reliably (so that statistical methods can be applied) and the choice of representative models (so that the findings will have as broad an applicability as possible).

Descriptive studies of drug use are intended to portray variations and trends in the extent, costs and quality of drug use among individuals and populations. As such, they play an essential role in identifying relevant questions and problem areas and they may provide an appropriate base for intervention; they do not, however, provide any explanation for the variations observed. Explanatory studies are intended to test hypotheses, generally relating to the causes of a particular phenomenon. In the present context, interest will focus on the influence of social factors on drug use, or conversely on the influence of drug use on society. Explanatory studies thus require a design that will permit inferences about causality.

Various designs have been employed. “Before/after” designs (pre-test/post-test) measure drug use before and after the introduction of an experimental variable and compare the change in drug use to that in a control group. This type of design is feasible, for example, when analysing the effect of various forms of information on drug use. In some cases, only an “after” measurement can be made; a “before” measurement is not possible. In this case, historical and parallel controls will be all important. Another possibility is a time series design, where drug use is repeatedly measured before and after an event occurs or a variable is introduced. This type of study is feasible, for example, when the effect of changes in health care systems is studied.

A more widely used design involves the comparison of different groups of people; an important tool here is multivariate analysis. For
the explanation of a complex phenomenon, such as the social aspects of drug use, multivariate analysis is very helpful.

A general issue in all quantitative studies concerns data collection. Some countries have population-based data banks containing drug utilization data; other data sources may be found in pharmacies or physicians' offices. In some research, hypothetical case histories have been used to analyse prescribing; the same case is presented to a series of physicians and their views as to how they would prescribe for the patient in question are recorded. An advantage of the method is that the case can be ideally constructed for its purpose and that each physician is confronted with precisely the same test situation; a disadvantage, naturally, is that intended and not actual behaviour is measured, and the two may differ. Intended behaviour is generally a good predictor of actual behaviour, however, and some studies have shown the reliability of the method (12).

These methods of data collection are not suited for studying actual drug use by individuals. In this case, interviews with the people themselves or diaries kept by them will need to be used.

The question of reliability and validity obviously arises, not only in the measurement of drug use but also in the collection of data on the social aspects of drug use. The most widely used method here is an interview or questionnaire. In general, however, the problem is that what people think or what they are willing to report is not necessarily the same as what actually happens, as shown by Avorn et al. (53).

Finally, a word of caution may be in place about the use of standardized questionnaires in cross-cultural research. As pointed out already, questions of health and illness and behaviour regarding treatment are strongly determined by the cultural context. Questionnaires developed and tested for validity and reliability in one country cannot therefore be transposed directly to another. Moreover, cross-cultural research requires a rigorous examination for conceptual, semantic and linguistic equivalence if groups are to be reliably compared. Recently, Hunt (79) showed the relevance of these issues in a cross-cultural study of health status, using a standardized questionnaire.

**Conclusion**

Drug use is influenced by (and in turn influences) a wide range of social, cultural and psychological factors; much remains to be known
before we can claim to have a complete picture of the social aspects of drug use. Studies in this field have evolved from mere descriptive accounts to investigations that provide explanations and put drug use into perspective. Most is known of the factors affecting prescribing by physicians and patient compliance, but even here a considerable gap in knowledge remains, notably with respect to behavioural factors. General influences, modifiable by administrative measures (such as commercial drug promotion and educational programmes), are fairly well defined. Self-medication is still a little understood aspect of drug use from a social-science perspective. The same applies to effects exerted at the macro-level by the health care system and the cultural environment; comparative research of an explanatory nature on drug use in different health care systems and cultural settings would be valuable here. Many different approaches, integrating theories and knowledge from the social sciences and medicine, pharmacology and pharmacy, are needed to understand the social forces involved in drug use. To some, it might seem that society is a confounding factor in the ideal drug use process. In fact, however, the complexity of the issue of drug use calls for a broad view, if the public interest is to be promoted by ensuring that drugs are appropriately used.

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Alongside the medical and social determinants of drug use, economic factors play an important role. Money has always been relevant to the use of medicines; throughout a great part of history, indeed, the best medicines were available only to the wealthy. In the industrialized world, that aspect receded in the twentieth century with the advent of national health services, reimbursement schemes and insurance funds; within a short time, medicines became available to all who needed them. But the idyll was not an unbounded one; in one country after another, the mounting costs of medical care soon became a source of concern to the societies that had decided that it must be universally available. By 1980, many countries were seeking to impose some form of constraint on the use made of the health services, and in particular on the provision of drugs (1). Although pharmaceuticals do not necessarily account for a very high proportion of total health costs in every country, they represent a form of expenditure that can be influenced in a way some others cannot, and they offer some prospects for economy that may be exploited without injuring the public interest.

The concern expressed about drug costs can come to the fore in different ways, relating variously to:

(a) the total sum spent on drugs as a part of total health expenditure, particularly when this appears disproportionate or is tending to increase;

(b) the price of certain individual drugs as compared with others;
(c) supposedly excessive prescribing, either generally or in certain situations;

(d) irrational prescribing, such as the widespread use of useless or inappropriate drugs.

Besides the health authorities, the other interested parties – the pharmaceutical industry, the pharmacists, consumer organizations and, to a lesser degree, physicians – have entered the debate to protect their goals and interests. Drug costs are now a matter of much controversy. The development of sound policies is nevertheless hampered by the lack of a clear basis on which to construct them.

One central problem that sometimes obscures the issue of drug costs or makes it hard to deal with is the lack of reliable data. On occasion, no figures at all are to be found; sometimes they are one-sided, suspect or incomplete, or they are misleading because of the methods and measures that have been used. Furthermore, the figures that do exist may be inaccessible because they are considered to be of strategic commercial importance.

To an increasing extent, these problems have been overcome in western Europe and in some other parts of the world. One may recall, after more than 20 years, that alongside the positive reasons that led to the establishment of the predecessor of the WHO Drug Utilization Research Group (DURG) in 1969, a negative reason was the unwillingness of the subscribers in various countries to a major commercial system for studying drug utilization to allow the data to be made available to the health authorities. Many of the sources the DURG ultimately came to use – notably those accumulated by health services and insurance funds for accounting purposes – happily provided reliable and detailed data on drug use, not only in medical terms but in economic terms as well. Taken alongside the data that the pharmaceutical industry does release, or that are produced in independent analyses, such information is often sufficient to form a clear view and to develop proposals for change.

**Costs, Benefits and Risks**

When discussing drug costs, one must realize that the acceptability of any measure to contain them must be measured in terms of its possible effect on public health. That consideration is a genuine one, although
it has sometimes been improperly used or exaggerated to protect vested interests. The basic rule is that expenditure on drugs should be related to what it buys in terms of public health; cost will need to be set against direct and indirect benefits and any proposed economy measure will have to be evaluated for its possible disadvantages or risks as compared with alternatives (Fig. 1).

**Fig. 1. Some elements to be weighed in a health economic balance on drug expenditure**

<table>
<thead>
<tr>
<th>Benefits to health</th>
<th>Economic effectiveness</th>
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<tbody>
<tr>
<td>Preventive and therapeutic effects:</td>
<td>Favourable influence on health and social welfare budgets</td>
</tr>
<tr>
<td>- reduced rates of complication, disability and mortality</td>
<td>through:</td>
</tr>
<tr>
<td>- more rapid restitution and symptom relief</td>
<td>- productivity gain</td>
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<tr>
<td>- enhanced quality of life</td>
<td>- reduced need for health and social care</td>
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</table>

<table>
<thead>
<tr>
<th>Risks to health</th>
<th>Economic costs</th>
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<tr>
<td>Lack of beneficial effects</td>
<td>Lack of efficacy</td>
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<tr>
<td>Adverse effects of interventions, whether transient or permanent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other direct and indirect expenses of, for example:</td>
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<tr>
<td></td>
<td>- drugs, diagnostic procedures</td>
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<tr>
<td></td>
<td>- related interventions</td>
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<td></td>
<td>- salaries of health professionals and social workers</td>
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<td></td>
<td>- hospital and primary health care, including transport</td>
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<td></td>
<td>- sick leave compensation</td>
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<td></td>
<td>- disability pension</td>
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<td></td>
<td>- premature death or unjustified prolongation of life</td>
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</tbody>
</table>
What is Spent on Drugs?

How much does society actually spend on medicines? The answer to that question can be presented in various ways – as a total amount per head, as a percentage of total health care costs, and as a percentage of gross national product (GNP). Are all these different approaches needed to obtain a clear idea of the position of any one country compared with others, or would not a single approach provide sufficient information? The answer is evident from Fig. 2, which demonstrates how the various approaches complement one another. This figure ranks the European Community countries according to the three approaches cited above, using the total expenditure in European Currency Units (ECU) per person, expenditure as a percentage of GNP and expenditure as a percentage of health care costs, based on consumer prices. The x-axis shows the rank of the countries according to total expenditure; thus Portugal spends overall least on drugs (lowest rank) and Germany (before the accession of the former German Democratic Republic) the most. As to expenditure as a percentage of GNP, however, Portugal belongs to a group of four countries (Belgium, France and Spain being the others) that occupy the rank 8.5 (they all spent 18%); yet if expenditure is taken as a percentage of health care costs, Portugal is one of the highest spenders. A note of caution is needed when interpreting Fig. 2, in that it presents only relative data and no absolute figures; moreover there is some doubt as to how the data in this comparison were calculated. The figure is presented merely to illustrate the present point.

Total expenditure is, of course, basically determined by the prices of products as charged by the manufacturer, the distribution and retailing costs (which together determine the retail price) and the quantities dispensed. Public health expenditure for drugs, moreover, depends on the scope of the reimbursement system in use. When studying these things – and particularly when seeking to learn from international comparisons – one must, however, be on the look-out for artifacts arising from differences in the way costs are defined in various countries; the exclusion or inclusion of tax figures, hospital prescriptions, drugs used in self-medication, for instance, can strongly influence the figures. For international comparison, the problem is compounded by the issue of fluctuations in exchange rates. Any description of drug expenditure must therefore be qualified in these respects, if it is not to be misleading.
Comparison between countries can be a useful tool; by determining whether the drug expenditure in one country is at all comparable to that in others in a similar phase of development, one may obtain important clues as to the rights and wrongs of the situation. Such international comparisons will often be made in terms of one currency, but this approach is complicated by exchange rates. For member states of the European Community, comparisons can be made in ECU, but this does not assist one in the (often highly instructive) comparison of Community with non-Community countries of northern and western Europe.

A useful technique – either nationally or in international comparisons – is to look at drug expenditure as a percentage of total health spending. This percentage is – even within Europe – surprisingly variable, as Table 1 shows. In some cases, a high percentage for drug
Table I. Drug expenditure as a percentage of health care spending

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>17.9</td>
</tr>
<tr>
<td>Denmark</td>
<td>10.6</td>
</tr>
<tr>
<td>France</td>
<td>17.8</td>
</tr>
<tr>
<td>Germanyb</td>
<td>10.9</td>
</tr>
<tr>
<td>Greece</td>
<td>20.2</td>
</tr>
<tr>
<td>Ireland</td>
<td>6.1</td>
</tr>
<tr>
<td>Italy</td>
<td>16.3</td>
</tr>
<tr>
<td>Netherlands</td>
<td>18.9</td>
</tr>
<tr>
<td>Portugal</td>
<td>17.9</td>
</tr>
<tr>
<td>Spain</td>
<td>17.8</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>12.8</td>
</tr>
</tbody>
</table>

° Based on data from Foreningen af Danske Medicinfabrikker (MEFA), 1988.

b Before the accession of the former German Democratic Republic.

Source: Kammrath (2).

costs can be explained by relatively low expenditure on other forms of health care; this is certainly the case for many developing countries, where many of the more sophisticated forms of health care are not available and prescribing may be the only widely available means of providing relief for illness. It is not, however, an adequate explanation for variations in western Europe; Switzerland, for example, is a country with a high percentage of drug expenditure but total health expenditure is also high. Furthermore, comparisons based on this approach will only be meaningful if both figures (drug expenditure and total health expenditure) relate primarily to a national health service of one sort or another; if there is a large private health sector and/or a large private drug market, such comparisons have to be drawn up in a different fashion. Even within western Europe, the balance between public and private expenditure on drugs varies considerably (Table 2).

Alongside such relatively rough data, one can also obtain rather more detailed evidence by analysing the quantities and the costs incurred per head (and the prices of drugs). One will, in that case, have to take into account differences in both costs of living and exchange rates, and remember that countries have different age structures, which can result in entirely defensible differences in patterns and levels of
Table 2. Public spending as a percentage of total expenditure on reimbursable drugs

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>53</td>
</tr>
<tr>
<td>Denmark</td>
<td>53</td>
</tr>
<tr>
<td>France</td>
<td>65</td>
</tr>
<tr>
<td>Germany(^b)</td>
<td>73</td>
</tr>
<tr>
<td>Greece</td>
<td>N.A.</td>
</tr>
<tr>
<td>Ireland</td>
<td>48</td>
</tr>
<tr>
<td>Italy</td>
<td>64</td>
</tr>
<tr>
<td>Netherlands</td>
<td>64</td>
</tr>
<tr>
<td>Portugal</td>
<td>67</td>
</tr>
<tr>
<td>Spain</td>
<td>67</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^b\) Before the accession of the former German Democratic Republic.

Source: Kammrath (2).

drug use. Yet another approach is to compare the unit costs of a standard sample of medicines in different countries.

The type of approach described up to this point will provide no absolute evidence of over- or underspending. For that purpose, one must use both economic and medical data, the latter relating to the quality of pharmaceutical care. Certainly, one must beware of making any broad statement about the amount of money that a society ought to spend on drugs, though one can examine that issue for a particular therapeutic class and come up with a reasoned estimate.

Such, then, are some of the techniques one can use and some of the pitfalls one must avoid. At this point, further methodological considerations are set aside for a critical look at some of the measures that can and have been taken to keep the costs of drugs within reasonable limits.

The Price of Drugs

The price of a drug should reflect what it is worth in public health terms; the need for the drug and its potential contribution to health should be central issues, to be set alongside purely financial considerations. To determine the value of a drug, three types of study can and have been performed, comprising cost–benefit analysis, cost–effectiveness analysis and cost–utility analysis (3, 4).
A cost–benefit analysis expresses costs and benefits purely in monetary units; the costs of two alternative (drug) treatments and the consequences in terms of productivity or sickness benefits may be compared, for example. An interesting example of this approach is an analysis by Fitton et al. (5) who determined the total costs to society of three conditions commonly treated in general practice. In cases of back pain, prescriptions accounted for only 12% of total expenditure, while sickness benefits accounted for 65%; the corresponding percentages for depression were 16% and 63%. For eczema, on the other hand (a condition not usually resulting in loss of working capacity), prescribing costs comprised 70% and sickness benefits 0%. This serves as a reminder that, even if an effective drug for back pain or depression were to increase prescribing costs two- or threefold, the net effect might be a saving to the community because of savings on sickness benefits.

In cost–effectiveness studies the consequences are measured in non-monetary units; the success rate(s) of various treatments may be compared, for example, in terms of the increase in life expectancy, while some newer techniques make it possible to measure such broad issues as health status (6) or quality of life (7).

Cost–utility analysis is the broadest approach; both costs and consequences are expressed in monetary as well as non-monetary units. A concept much used in this context is the quality adjusted life year (QALY), which provides one parameter to measure an increase both in life expectancy and in the quality of life (3,8,9). Although this concept may be helpful in clarifying the issues at hand, one should beware of giving economic evaluation the upper hand. The valuation of different states of health or conditions after medical intervention is far from perfect and based on a series of – often moral – assumptions. Moreover, information as to the norm is often inadequate. Questions remain about the feasibility of applying to individuals ratings derived from group studies (10).

Of these three types of study in the field of drug use, the emphasis to date has been on cost–benefit studies (11). Nevertheless, advances in the development of reliable and valid measures for health status and quality of life will facilitate the broader approaches of cost–effectiveness and cost–utility analyses. Which of these last two approaches is to be preferred depends on the problem studied. If a new drug is
cheaper than those that have gone before it, but the results of clinical trials suggest that it is as effective and safe, a cost–effectiveness study is adequate, although it may need to be revised as further experience with the drug accumulates. On the other hand, if the new drug is more expensive, but extra therapeutic benefits or fewer adverse reactions are expected, the cost–utility approach should be used. Naturally, economic appraisal can only be as good as the medical appraisal on which it is based.

When one compares the prices of individual drugs today in different countries one finds a very marked variation, showing the distance yet to cover before attaining prices that reflect the worth of these drugs in terms of public health. Adriaenssens & Sermeus (12), comparing price levels in the European Community, show that those in Germany, Ireland and the Netherlands are overall about 2.5 times higher than in the cheapest country, Spain (Table 3); the price comparison used in that study is based on a basket of products, representing the “top 20” pharmaceuticals in terms of total sales value and the “top 10” in terms of volume, identical products from the same firm in each country being selected.

Although some companies apparently prefer to keep drug prices in various countries at a similar level (13), others do not. The examples given in Table 3 show how extreme the variations in the price of a single product can be. Quite valid reasons may exist for why the price of a medicine should differ somewhat between countries, but variations of the size shown here between countries at comparable levels of economic development raise questions.

Although the figures in Table 3 are somewhat dated, there is no indication that the situation has changed dramatically since they were recorded. One might, on the other hand, expect prices to attain a more similar level, if the European Community succeeds in creating an integrated pharmaceutical market after 1992.

The price of a drug must clearly be allowed to carry not merely the costs of its own development, but also the costs of the basic and/or applied research programme that produced it and the costs of other but unsuccessful projects within the same research organization. It must also cover the general overhead costs of the company and leave a reasonable margin for promotion and for return on investment. Here, again, the inaccessibility of data raises fundamental problems. To decide what is a fair price for the company, it is important to have adequate data on profits, and research and promotion costs within the
Table 3. Examples of extreme price differences within the European Community, in ECU (January 1986)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC code</th>
<th>Trade name</th>
<th>Average</th>
<th>Minimum (country)</th>
<th>Maximum (country)</th>
<th>Price differential (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M04AA01</td>
<td>Zyloric</td>
<td>18.95</td>
<td>4.52 (Spain)</td>
<td>46.95 (Ireland)</td>
<td>938</td>
<td></td>
</tr>
<tr>
<td>N05AX04</td>
<td>Dogmatil</td>
<td>9.21</td>
<td>2.12 (Italy)</td>
<td>18.43 (Netherlands)</td>
<td>769</td>
<td></td>
</tr>
<tr>
<td>C04A</td>
<td>Strugeron forte</td>
<td>18.56</td>
<td>4.15 (Portugal)</td>
<td>34.86 (Ireland)</td>
<td>739</td>
<td></td>
</tr>
<tr>
<td>C03A</td>
<td>Dytide H</td>
<td>6.05</td>
<td>1.53 (Spain)</td>
<td>12.16 (Germany&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>697</td>
<td></td>
</tr>
<tr>
<td>N05BA06</td>
<td>Temesta</td>
<td>3.40</td>
<td>1.20 (Italy)</td>
<td>9.16 (Germany&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>663</td>
<td></td>
</tr>
<tr>
<td>N05AD01</td>
<td>Haldol</td>
<td>8.31</td>
<td>2.22 (Portugal)</td>
<td>16.93 (Germany&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>662</td>
<td></td>
</tr>
<tr>
<td>N02BA01</td>
<td>Aspirine</td>
<td>0.95</td>
<td>0.30 (Spain)</td>
<td>2.20 (Germany&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>630</td>
<td></td>
</tr>
<tr>
<td>C01DA08</td>
<td>Cedocard</td>
<td>13.42</td>
<td>3.64 (Spain)</td>
<td>26.37 (Netherlands)</td>
<td>624</td>
<td></td>
</tr>
<tr>
<td>A10BB01</td>
<td>Euglucon</td>
<td>6.34</td>
<td>1.92 (Spain)</td>
<td>13.59 (Ireland)</td>
<td>608</td>
<td></td>
</tr>
<tr>
<td>M01AB01</td>
<td>Indocid</td>
<td>6.06</td>
<td>1.70 (Italy)</td>
<td>11.85 (Netherlands)</td>
<td>597</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Before the accession of the former German Democratic Republic.

Source: Adriaenssens & Sermeus (12).

firm. It is anything but simple to obtain such figures; fundamental considerations of confidentiality apart, the estimates are complicated by international operations and the blending of pharmaceutical with chemical, cosmetic, food and other operations; the available figures for any particular company thus often relate to that company’s total
performance in a number of different industrial sectors. It is not surprising to find marked discrepancies in the results obtained when different interested parties analyse profitability and costs.

One good battery of techniques for a critical analysis of profits is that provided by the 1985 report of Canada's Commission of Inquiry on the Pharmaceutical Industry (14). Using four different approaches (namely, profitability after taxes on total income, after taxes on equity, and before and after taxes on capital employment), the Commission found good evidence that profits in Canada had been fairly consistent between 1968 and 1982. Notable in that study is that the profitability of the pharmaceuticals industry clearly exceeded that of manufacturing industries as a whole. These figures from Canada refute the often heard argument that the pharmaceuticals industry is in a difficult situation and that attempts to reduce either drug prices or drug consumption would endanger its future.

The other argument heard against price reduction is that it would put an end to innovative research. Proposals have been developed, however, to reward genuine innovation as measured, for example, on the Dukes/Lunde innovation scale (15). The concept is that a drug that is truly innovative, in terms of clinical usefulness, may be accorded a price that is x-times higher than one at a lower level of clinical innovation. Another approach is to express the degree of innocuity of a drug in public health terms, using the methods of cost-effectiveness or cost-utility analysis described before. Thus, the more prone a drug is to cause adverse effects, including social and economic adverse effects, the lower its value to the community. The assessment will have to be adapted, however, as experience with a drug increases.

**Distribution Costs**

Distribution systems and costs, again, vary widely. The total proportion of drug expenditure that reflects wholesale and retail margins is high, commonly 30-45% of the retail price; both wholesale and retail margins vary greatly from one country to another (12, 16-19). Some countries, such as Japan and Spain, have taken measures to reduce these margins (20). A critical reappraisal of regulations relating to pharmacies may be needed. Some pharmacists may earn unreasonably high profits by supplying products at prices agreed within a health insurance scheme, but obtaining these products by parallel import at much lower prices. In the Netherlands, the system of agreed prices was
abandoned in July 1987, despite protests from the pharmaceutical world; the pharmacist may now retain a third of the price difference between a branded product and a cheaper equivalent, thus encouraging the use of cheaper products. The increasingly active involvement of pharmacists in the process of drug use (see Chapter 6) deserves to be remunerated, however; in many instances, their active involvement saves the community considerable sums. Finally, it would be worthwhile to compare the costs of distribution and retailing in countries where these are in public hands with those in countries where wholesale and/or retail pharmacy is in private hands.

Reimbursement and Payment for Drugs

Most industrialized countries have some form of reimbursement for pharmaceuticals. As with all other aspects of drug expenditure, the differences from one country to another are considerable. Five major characteristics can be distinguished (18).

1. *The method of payment.* The costs of drugs may be paid directly by an official body, or the patients themselves may pay the costs and then be reimbursed. In Europe, indirect payment or mixed systems are usually found.

2. *The beneficiaries.* Some schemes apply only to a part of the population (such as lower income groups or chronic invalids), others to the entire community.

3. *Categories of reimbursable drugs.* Many countries reimburse only a selection of prescription drugs. The most usual criterion for selection is the therapeutic usefulness of a drug or the seriousness of the disorder it is used for. The results of applying this general principle, however, differ widely from country to country. Another approach is to select for reimbursement only those drugs whose cost is acceptable when assessed in terms of their usefulness or as compared to alternative drugs.

4. *The structure of reimbursement to the patient.* Three main systems exist. The patient may pay a certain percentage of the retail price, which means that the patient's contribution increases with the price of the drug (for example, in Belgium or France). In other
schemes, a fixed amount must be paid for each item supplied. Finally, a combination of the two systems is in use in some countries.

5. The reimbursement level for drugs. The proportion of costs reimbursed is the same in some countries for all reimbursable drugs; in others, it varies from one class of drugs to another according to their therapeutic usefulness.

Even when limiting the comparison to such major points, one finds very great differences between countries. The only common element is a universal unwillingness to pay all drug costs from the public purse; in one way or another restrictions are always imposed. They may be created by ministerial decree, by formulary committees, or by scientific bodies set up by national health insurance schemes to decide which drugs have sufficient merit to be worth paying for.

A limited list of reimbursable drugs (characteristic no. 3 above) is an increasingly important tool for such restriction. In their most stringent form, limited lists allow payment from the public purse only for those drugs that provide the best value for money. Even the most liberal approach is likely, however, to be designed to avoid paying the costs of trivial, ineffective or unproven therapy. Each of these three possibilities merits some discussion.

Trivial therapy is that for very minor self-limiting disorders that can often be handled without giving drugs at all or by simple self-medication with over-the-counter remedies paid for by the user. In the 1980s, a number of countries found it necessary to restrict public expenditure on drugs used for such purposes, notably the Netherlands (1982), Germany (before the accession of the German Democratic Republic) (1983), Denmark (1983) and the United Kingdom (1985). The introduction of this approach in Germany (which, in fact, chose to issue a negative list of drugs ineligible for reimbursement) appears to have been successful: a drastic fall in the number of prescriptions for products on the negative list was recorded after nine months (21).

Paying for ineffective therapy is a waste of money: if the physician wishes to give a placebo, there are cheaper ways of providing one. The major tool for preventing such waste is, of course, a drug regulatory system, which will provide a proper premarketing evaluation of the efficacy and safety of all drugs, old or new. Most countries today have such systems but, as pointed out in Chapter 2, many have not yet re-evaluated the older drugs marketed before the system was created.
The issue of unproven therapy largely centres around the prescribing of registered drugs for indications in which their usefulness has not been proved or accepted by the regulatory agencies. Most countries take the view that physicians are free to use a licensed drug for any such purpose at their own discretion and risk. Undoubtedly, this reflects the importance placed on the autonomy of the physician, which is traditionally a core value in medicine. A large part of the cost problem, however, is the widening of the field of drug use (22). Cimetidine, for example, was found to be widely used for mild gastric discomfort which would respond to antacids, diet or other simple measures (23). Tranquillizers are widely used for the non-pathological stress of everyday life (24). Discouraging such use is perhaps more a question of education than of refusing payment under a health scheme. Nevertheless, the latter approach is used in Australia and New Zealand with success and should therefore not be ruled out.

The imposition of prescription charges (characteristic no. 4 above) is another important aspect of reimbursement policy; it was indeed one of the first measures used in the field of cost containment. An overview of the situation in the European Community countries is provided in Table 4. In the United Kingdom – which appears to have the oldest system of prescription charges – costs show a saw-toothed pattern with an upward trend, temporarily flattened by each increase of prescription charges but very soon resuming its upward course (25). More thorough analysis of events in the United Kingdom between 1979 and 1983 revealed a decrease in the number of prescribed items per head by 7.5% in the population group that paid charges, but an increase of 1% in the population group exempt from charges; during this period prescription charges increased tenfold in terms of price but sixfold in real terms (26). In the 1980s, other European countries either increased prescription charges (Belgium, France, Germany) or introduced them for the first time (the Netherlands, Norway).

Experience with the most recent cost-containment measures (limited lists and prescription charges) is so far mixed. In the Netherlands – where the introduction of a negative list in 1982 was followed a few months later by the imposition of prescription charges – the initial fall in drug expenditure was more than offset by the increase a year later (27, 28). In the United Kingdom, the introduction of a selected list in 1985 seemed to have been successful in terms of reducing costs (29); later analysis, however, showed an increase in long-term prescriptions (30). There are, moreover, indications of a shift from low-cost
Table 4. Average contribution made by patients
towards the retail cost of certain reimbursable proprietary
products available in all European Community countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Average contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany(^a)</td>
<td>12.4</td>
</tr>
<tr>
<td>Netherlands</td>
<td>13.2</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>18.8</td>
</tr>
<tr>
<td>Greece</td>
<td>26.6</td>
</tr>
<tr>
<td>Portugal</td>
<td>32.0</td>
</tr>
<tr>
<td>Italy</td>
<td>33.1</td>
</tr>
<tr>
<td>Spain</td>
<td>34.9</td>
</tr>
<tr>
<td>Belgium</td>
<td>42.2</td>
</tr>
<tr>
<td>France</td>
<td>43.4</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>51.6(^b)</td>
</tr>
<tr>
<td>Denmark</td>
<td>56.2</td>
</tr>
<tr>
<td>European Community</td>
<td>33.1</td>
</tr>
</tbody>
</table>

\(^a\) Before the accession of the former German Democratic Republic.

\(^b\) In the United Kingdom about 60% of the population do not have to pay.

Source: Sermeus & Adriaenssens (19).

non-permitted items to high-cost permitted items on the approved list. A study in one computerized group practice compared prescribing before and after the introduction of the limited list in the United Kingdom (31) and found different results for different drug groups affected by the limited list. The prescribing rates for laxatives, benzodiazepines and analgesics did not change; prescribing for vitamins, and cough and cold remedies decreased, but prescriptions for iron and antibiotics increased; the use of H\(_2\) blockers increased, despite the lack of change in antacid prescribing rates. A questionnaire investigating how physicians cope with the list in the United Kingdom found that most experienced few difficulties. To find alternatives for cough and cold remedies, as well as vitamins, was experienced as difficult, however, and many patients were dissatisfied with alternative means of dealing with cough and colds. Physicians also had to find alternatives for those tranquillizers that were no longer permitted, but they reported no difficulties in doing so (32).
In the Netherlands, too, shifts in prescribing patterns occurred, in this case with nonsteroid anti-inflammatory drugs being used instead of cheaper analgesics (33). To reduce the costs for patients, prescriptions were issued for longer periods of time, thus avoiding repeated prescription charges (34); as a countermeasure a limitation had to be introduced on the periods for which drugs could be prescribed.

Finally, from Ireland, there is some evidence that mefenamic acid was increasingly prescribed once paracetamol and dextropropoxyphene were no longer reimbursable; a similar restriction on cough syrups seems to have led to the increased prescribing of carbocisteine (35).

The overall impression from the reactions so far to this type of cost-containment approach is that if the needs of everyday medical practice are taken insufficiently into account, the measures will defeat their own ends. Physicians — sometimes because of patient pressure — will look for solutions that may not only be uneconomical, but also introduce unnecessary medical or toxicological risks. Such unintended consequences may be prevented by consulting physicians more closely and involving them when decisions on prescribing are to be taken; some experiments of this sort have already proved successful (36, 37). Moreover, it is essential that physicians see that the new policies bring benefits to the community that are more than merely financial; doctors are, after all, more interested in patient- and disease-related outcomes than in controlling costs (38). The public needs to understand the potential benefits of the measures and to comprehend that a change in name (or price) need not imply a change in effect. Patients have definite ideas about their medication (see Chapter 6), which have to be taken into account if measures are to be effective. A number of other cost-containment measures have been proposed or tried. Positive financial inducements, such as higher fees for general practitioners when they collectively reduce referral rates or avoid unwarranted expenditure on medicines and physiotherapy, have been tried in Bavaria without apparent success (Herbert Zöllner, personal communication, 1985). Imposition of penalties for heavy prescribing has been proposed on many occasions, but it is not clear how effective they can be. Hospital formulary committees are increasingly active in many countries and have proved to be effective both in reducing costs and in promoting the quality of care (39, 40). The abolition of the dispensing physician has been suggested by some, the idea being that physicians who stand to earn on the sale of drugs they prescribe themselves, will
be inordinately heavy prescribers. In fact, however, dispensing general practitioners in the Netherlands (16% of all physicians) have been found to be relatively economical prescribers. In Switzerland, the curtailment of drug-selling privileges enjoyed by Swiss physicians proved to be marginally cost-increasing instead of cost-saving \((I)\).

Some other specific measures that have been proposed as a means of containing costs remain untried; others have not been systematically evaluated and some have been rejected primarily for economic reasons. Examples of such measures are:

- dispensing economical pack sizes
- limiting prescribing by general practitioners to certain drugs
- imposing requirements for generic prescribing or substitution
- limiting the number of drugs per prescription
- limiting the periods for which prescriptions can be valid
- restricting prescribing in response to telephone requests
- restricting the automatic repeating of prescriptions
- monitoring drug budgets per hospital.

Information and Education

Compulsory methods alone, such as those taken within the reimbursement system, do not ensure that the money available will be used in the public interest. In the long run, improvements in prescribing quality, with both the elimination of waste and the reduction of risk, will be essential. The first and obvious step is to include economic considerations in the training of physicians, as well as to improve their training in drug therapy as a whole.

Various other means are used today to encourage appropriate and economical prescribing, through the provision of information. Independent or official drug bulletins, now widespread, are designed mainly to improve the quality of prescribing, although some confront the physician with the costs of the drugs they review. The \textit{Drugs and therapeutics bulletin} in the United Kingdom is one example. In Germany, the \textit{Transparenztelegramm}, issued annually, provides exact prices. In the Netherlands, all physicians receive annually an updated copy of a drug formulary (the \textit{Farmacotherapeutisch kompas}), which indicates first choice drugs and drug prices within therapeutic classes and emphatically indicates which products should not be used on the basis of both cost and merit.
A new development is the publication of what one might term “anti-advertisements”, resembling commercial promotion in style but designed to stress the need for critical prescribing and the avoidance of waste; evidence is increasing that this approach can be successful (41). Parallel experiments with “counter detailing” or “anti-salesman” indicate that this may be an even more effective and efficient way of putting such messages across (36). What emerges from various of these ventures is that, if independent information is to be effective, it must be at least as clear, emphatic and understandable as the information provided by the pharmaceuticals industry.

**Conclusion**

Drug costs have, until comparatively recently, featured only to a limited extent in many drug utilization studies; the view of many physicians conducting such studies was originally that matters of expenditure should be considered elsewhere, by policy-makers and the pharmaceuticals industry. Increasingly, however, researchers have come round to the view that therapeutic trends must be looked at from the economic as well as the medical point of view. Drug utilization studies are, in this as in other areas, vital tools if one is to identify the problems and then evaluate the efficiency of the steps taken to solve them. Drug utilization studies can also make an important contribution by striking a balance between the benefits and risks of drug use; as such they can support the development of rational and integrated drug policies. A major challenge in the near future for the development of such a drug policy is the planned integration of the market of the European Community; unless policy-makers have reliable and impartial information at their disposal, it will be hard for them to ensure that the money available will indeed be used to produce the greatest good.

**References**


Most countries already have – or are about to have – a system of drug legislation that is intended to ensure that the population is supplied with safe and efficacious drugs. Not even the most developed and stringent drug control system can guarantee, however, that no new effects or adverse reactions will be detected after the approval and marketing of a drug; indeed it would be highly exceptional if such new knowledge did not appear after that time. Unwelcome developments may relate to efficacy as well as to adverse effects and interactions; the early promise a drug may have shown during clinical trials is by no means always borne out when it is used on a much larger scale in the field.

Concern is increasing that much prescribing may be unnecessary, inappropriate or irrational. It is therefore important that at all levels it is known what drugs are being prescribed, how much is being prescribed, by whom, for what reason and at what cost. This information, set alongside what is known about the merits and limitations of the drug, is a necessary basis for determining drug policies and for assessing the effects of such policies in the field. Health authorities need this basic information as much as drug committees, teachers in clinical pharmacology, prescribing doctors and others who take decisions and play a role in ensuring the rational use of drugs.

To date, the means to carry out a complete “therapeutic audit” are not available, either in industrialized or developing countries. Many data can be gleaned, however, from existing information sources (such as sales statistics and prescription data) even where they have originally been compiled for other purposes (see Chapter 4). This chapter confines itself to the influence that findings from drug utilization studies have had on the decisions health authorities have made relating
to rational drug use, illustrating this by considering case histories from Czechoslovakia, Ireland, Spain and Sweden.

Czechoslovakia

Czechoslovakia is an interesting example of a country where the health authorities have been not only users of drug utilization data but also prime movers in its production and distribution. Drug consumption has been systematically investigated in Czechoslovakia since 1952. Today, drug utilization data form part of a computerized database located at the State Institute for Drug Control in Prague, which is responsible for the approval of drugs, for drug monitoring and, last but not least, for evaluating the therapeutic efficacy of drugs in clinical practice as well as their influence on the population as a whole. In interpreting all the data presented from Czechoslovakia, the reader should of course bear in mind that the country is now going through a major process of change; most of the information presented here dates from a period before that change.

Macro-data on drug supply, including, for example, records of wholesale drug deliveries to community and hospital pharmacies, are stored in the database. They are complemented by other types of data, relating to the health status of the population and to health care in general; one will, for example, find figures on the prevalence of diabetes alongside information about the treatment that is employed, thanks to the fact that annual reports on registered patients from district and regional dispensaries throughout the country are collected by the relevant division of the Ministry of Health.

The example of diabetes may be taken to illustrate some possibilities and uses of the system. In Fig. 1 and 2, the consumption of insulin and oral antidiabetic drugs in Czechoslovakia is compared with that in a number of other countries over the period 1975–1984. The annual meetings of the Czechoslovak diabetologists are the most appropriate forum in which these data can be presented and discussed and this has been regular practice. At the same time, more detailed information on district figures is distributed to leading national and regional specialists so that they can conduct a detailed and continuing analysis of the trends and the persisting differences in local prescribing patterns.

Utilization data can also be used to study medical situations that are subject to rapid change, as is shown by the case of respiratory infections. Figures on the incidence of acute respiratory disease are
registered by epidemiologists at weekly intervals. As will be seen from Fig. 3 and 4, this information can be set alongside figures on the monthly dispensing of two types of antibacterial agent (broad-spectrum penicillins and co-trimoxazole). All this feedback is continuously presented at meetings of antibiotic centres and to the Central Committee for Rational Drug Therapy to provide a basis for their own continuous analyses of antibiotic policy.

Fig. 1. A comparison of the consumption trends of insulin in Czechoslovakia and the Nordic countries, 1975–1984

Source: Štika et al. (1).

* Antibiotic centres are advisory and technical institutions responsible for performing specialized laboratory examinations, maintaining surveillance of resistant microorganisms, and planning and ensuring the supply of certain antibiotics that may only be prescribed on their recommendation.

* Committees for rational drug therapy operate at all regional and district health care institutions, which are responsible for the provision of health care in their catchment area. The Central Committee for Rational Drug Therapy (at the Ministry of Health) gives expert professional guidance to committees at lower levels. The guidelines used by these committees are based on the principle that a therapy can be regarded as rational only if, in the light of the latest medical knowledge currently available, it is likely to achieve the desired therapeutic effect in the quickest and simplest possible way.
Fig. 2. A comparison of the consumption trends of oral antidiabetic drugs in Czechoslovakia and the Nordic countries, 1975–1984

Source: Štika et al. (1).

Fig. 3. A comparison of the incidence of acute respiratory disease with the monthly dispensing of broad-spectrum penicillins in Czechoslovakia, from January 1986 through December 1987
The fact that it is possible to follow not merely broad trends but also the prescribing patterns of individual drugs or drug groups, as defined by the ATC classification, is of considerable value. An example is a comparison of the use of benzodiazepine anxiolytics in 50 Czech hospitals that was undertaken in 1985. The data, expressed in terms of DDD per 100 bed-days, were tabulated and sent to departmental heads who were asked to examine the findings and comment on them.

According to their analyses, age and principal diagnosis were the main determinants of benzodiazepine consumption; it appeared to be little influenced by attempts to provide physicians with therapeutic guidance. Despite this, answers to additional questions revealed that medical departments with lower consumption levels reported twice as many postgraduate courses on the rational use of benzodiazepines and half the frequency of drug applications given at the discretion of nurses than did departments with a higher level of consumption (2).

The Ministry of Health obtains the bulk of its data on drug use, structural trends and changes in national drug utilization through the Central Committee for Rational Drug Therapy, and the data are broken down to regional and even district levels. The Central Committee is one of a network of such committees for rational drug therapy, which have been working successfully throughout Czechoslovakia for decades. In individual regional or district health care institutions, the prescribing pattern of physicians is followed and discussed by the appropriate committees for rational drug therapy directly with prescribers. This has contributed significantly to an improvement in the professional standard of pharmacotherapy throughout the country. An example of the influence exerted in this way is provided by a study of changes in the proportion of different cardiac (including parenteral) products in total consumption (Fig. 5).

To solve certain other problems connected with therapeutic drug use, other committees have been established under the auspices of the Ministry of Health, one of the most important being the Committee for Adverse Drug Reactions. The number of reports received has increased year by year, attaining 4232 in 1986 (4). Evaluation of the incidence of adverse reactions remains a difficult part of the evaluation of drug safety, however; the current prospect of having data both on drug consumption and on adverse reactions in one computerized system is very promising.

As pointed out above, the concentration of drug utilization figures at a single national centre does not benefit only the process of planning
Fig. 4. A comparison of the incidence of acute respiratory disease with the monthly dispensing of co-trimoxazole in Czechoslovakia, from January 1986 through December 1987.

Fig. 5. The change in the use of different cardiac glycosides as a proportion of total consumption in Czechoslovakia, 1977–1987.

Source: Sechser et al. (3).
and organization at the health ministry. One of the other groups to benefit comprises people involved in postgraduate medical education at various levels, including those who teach clinical pharmacological principles to the general practitioner. Such teaching, backed by firm figures on current patterns of drug use as a means of identifying problems and opportunities for improvement, provides an exciting starting point for promoting better prescribing and habits of drug use. Access to such data also offers an exciting opportunity for research into the factors that affect (or should affect) the prescribing of drugs to the individual. In fact, pharmacoepidemiology is truly emerging as an important interdisciplinary field of study. The interdisciplinary approach— involving clinicians, pharmacologists, pharmacists, epidemiologists, statisticians and sociologists—must in time form the basis of such work not only locally, regionally and nationally, but also internationally.

Ireland

In Ireland, two main types of drug utilization study are carried out by the National Drugs Advisory Board:

(a) a continuously maintained record of all drugs prescribed in a specifically designated group of people:

- occupants of specified hospital beds in general medical wards (at present in two large teaching hospitals);
- attenders for consultation with specified general practitioners;

(b) special intensive monitoring of all patients for whom one or more specified drugs have been prescribed.

An example of the first type of study is an investigation involving 70 general practitioners located throughout Ireland. Information was returned on a total of 20,444 patients seen in their practices during the relevant period. Of these, 19% were aged up to 15 years, 30% between 15 and 44 years, and 21% and 24%, respectively, between or beyond the ages of 45 to 64 years. These proportions reflect the age distribution of the population in general. Of the totals for all age groups, female patients represented about 1.5 times the male total (61:39). In rural areas, however, the sex ratio of patients was almost equal, while in the age group up to 15 years the male:female ratio was 2:1.
Table 1. Proportional usage figures for the main categories of drug used in Ireland (sample period)

<table>
<thead>
<tr>
<th>Category of drug</th>
<th>Total usage recorded (%)</th>
<th>Age group with greatest usage (years)</th>
<th>Total usage in that group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-infectives</td>
<td>15.2</td>
<td>0 - 14</td>
<td>35.0</td>
</tr>
<tr>
<td>Tranquillizers/antidepressants</td>
<td>6.7</td>
<td>45 - 64</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 65</td>
<td>12.5</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>2.5</td>
<td>15 - 44</td>
<td>4.0</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>7.8</td>
<td>≥ 65</td>
<td>15.8</td>
</tr>
<tr>
<td>Diuretics</td>
<td>5.9</td>
<td>≥ 65</td>
<td>12.5</td>
</tr>
<tr>
<td>Analgesics°</td>
<td>7.1</td>
<td>45 - 64</td>
<td>8.7</td>
</tr>
<tr>
<td>Antitussives/antihistamines</td>
<td>2.0</td>
<td>0 - 14</td>
<td>4.5</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>3.0</td>
<td>0 - 14</td>
<td>4.5</td>
</tr>
<tr>
<td>Gastrointestinal drugs</td>
<td>4.9</td>
<td>≥ 45</td>
<td>4.8</td>
</tr>
<tr>
<td>Advice/referrals</td>
<td>15.1</td>
<td>0 - 14</td>
<td>18.0</td>
</tr>
</tbody>
</table>

° Nonsteroidal anti-inflammatory drugs, acetylsalicylic acid and paracetamol.

Proportion of usage figures for the main therapeutic categories of drug prescribed over the specified period were as listed in Table 1. There was little difference in pattern between urban and rural areas. The drug usage patterns within a few of the age groups are worth looking at in greater detail.

In the case of the tranquillizer/antidepressant category, it was found that, in the group aged 45–64 years, 56% of the prescriptions were for tranquillizers, 22% for hypnotics, and 22% for antidepressants. In the group aged 65 and over, the proportion of tranquillizer prescriptions was much the same as the survey average (51%) but higher for hypnotics at 33%, and lower for antidepressants (16%). A further breakdown of the tranquillizer group reveals that one fifth of the prescriptions were for the major tranquillizers (such as neuroleptics), reflecting the proportion of schizophrenic patients being managed within the general community.

A review of the usage of cardiovascular agents revealed that the cardiac glycosides and diuretics are the most commonly prescribed drugs in this category for the elderly, with coronary vasodilators also prominent. By contrast, in the group aged 45–64 years, for whom hypertension is of greater significance, the diuretics, beta-adrenoceptor blockers and then peripheral vasodilators (adrenoceptor blockers), in that order, represent the principal components. The angiotensin-
converting enzyme (ACE) inhibitors have been restricted to consultant use until quite recently and consequently did not figure significantly at the date of this report.

Therapeutic response was classified as acceptable in 68% of patients receiving tranquillisers/antidepressants and in 82% of those receiving cardiovascular drugs (91% in the case of the people aged 65 and over, and 73% in the group aged 45–64 years).

In the management of hypertension in the group aged 45–64, 13% responded to diuretics alone, 21% to beta-adrenoceptor blockers alone and 20% to a combination of diuretic and beta-blockers. Vasodilators were used satisfactorily in 20% of patients, often as part of a combination.

Side effects were recorded in 1.5% of the patients treated.

An example of the second type of study (intensive monitoring) is an investigation of the use of captopril in the management of hypertension. This ACE inhibitor, as pointed out above, was initially introduced for hospital consultant practice only (for the first two years after the new drug was approved). Once experience had been gained there, the product was introduced into general practice use.

During the period of consultant use, the authorized indications were only the management of hypertension and of congestive heart failure. Over the two-year period of monitoring, experience was gained from use in just over 600 patients with moderate to severe hypertension. Of the 600 patients treated, 184 responded satisfactorily to captopril alone and 373 to a combination of captopril with a diuretic. In the remainder, response was inadequate, the drug had to be discontinued because of unacceptable adverse effects, or patients were lost to treatment.

After completion of this monitoring study, the use of captopril in the management of hypertension was extended to general practice, while intensive monitoring continued. As a result of the experience gained in the consultant phase and in other countries, a number of amendments were made to the conditions for use of the product. The most important were the following.

1. The recommended dosage was reduced to 25 mg thrice daily, with a total dose rarely to exceed 100 mg. The elderly were usually controlled on 50 mg daily.

2. Where higher doses were required, a diuretic should be added; a thiazide was usually preferred, but a “loop” diuretic should be used in the presence of renal impairment.
3. Use in patients with renal impairment should generally be avoided, in view of the potential for proteinuria and neutropenia.

Intensive monitoring then continued into the phase of use in general practice. In the next three years, a total of 1743 patients received captopril for the control of moderate hypertension; 38% of those treated were controlled long term on 50 mg daily, 22% on 75 mg and 16% on 100 mg. Response to therapy was very good in 32% after 5–6 months' therapy and remained so for at least 12 months; it was good in 50% after 3 months and maintained for at least 12 months. A total of 1650 patients continued therapy after 12 months. Some 90% were within the age range 41–75 years.

Captopril was added to the pre-existent diuretic therapy of 40% of patients and to the diuretic plus beta-adrenoceptor therapy of 10% of patients.

Some 18% of patients were withdrawn from treatment (1% lost to follow-up, 0.5% because of lack of efficacy, 2% because of significant adverse effects, 1% by death, and the remainder because of poor cooperation, etc.). Side effects included cough, postural hypotension, fatigue, arthralgia, mild depression and dysgeusia.

Spain

Drug utilization in Spain has undoubtedly been influenced by the past history of its pharmaceuticals market and, in more recent years, by the intervention in this market of the health authorities. Any discussion of the topic should therefore begin with a brief word on regulatory developments.

The drug regulatory process in Spain

Although the legal registration of drugs in Spain dates back to 1920 and was revised in 1963, little provision was made at those times for the critical assessment of the products being registered. Comprehensive legislation for the registration of new and older products according to present-day standards appeared in 1973, and involved a progressive increase in technical requirements. The pharmaceuticals market in 1973 still comprised 27,000 products, many of which were fixed-dose combinations with little evidence to substantiate the claims made for them. The task of the present Drug Regulatory Authority has been to review this large and complex pharmaceuticals market to ensure the
efficacy, safety and quality of the medicines available in Spain as a first step towards the rational use of drugs. In 1973, a study of the medicines in greatest use within the national health service (Seguridad social) led to the withdrawal of a large number of fixed-dose combinations. The Drug Regulatory Authority took another major step forward in 1983 by initiating a phased programme (Prosereme) to review the entire pharmaceutical market (Table 2). This project is intended to ensure that Spain complies with the European Community agreements in this field. Clinical pharmacology is the specialty capable of making the greatest contribution to this type of work and appropriately qualified personnel were recruited in 1984 to carry it out.

Recent measures have included the establishment of standards and approval procedures for clinical trials. The responsibility for this matter was initially placed with the national health authorities, but devolution to local committees is now under way.

Sources of drug utilization information
The most important source of information on drug utilization that is routinely used by the health authorities is the drug data bank. This data bank emerged from the data collected to reimburse physicians and pharmacists within the national health service. Gradually the quantities and type of data collected increased in complexity, and the data bank is today maintained and managed in the drug evaluation area of the General Directorate of Pharmacy. It serves its original purpose but also a number of others. The bank comprises four databases:

- ESPES, which contains basic information on the pharmaceutical products available in Spain;
- ECOM, which contains consumption data on pharmaceutical products reimbursable by the national health service;
- PACTIV, which contains pharmacological information on all drugs marketed in Spain and their active ingredients;
- TRAMIT, which contains pharmacological and administrative information relating to the registration of the pharmaceutical products for use in the country.

These four databases supply information that can be used in the evaluation of new drugs, in the review of older products according to European Community procedures, in price control procedures, in the
Table 2. Programme for the selective reassessment of medicines (Prosereme) in Spain

<table>
<thead>
<tr>
<th>Phase and period covered</th>
<th>Drugs/therapeutic group assessed</th>
<th>Number of products subject to restrictive decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Withdrun</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983–1984</td>
<td>1. Amphetamines and derivatives as anti-obesity agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Inorganic arsenic compounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Clioquinol (oral forms)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Dihydrostreptomycin (parenteral)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Strychnine</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>1. Butylpyrazolidines</td>
<td>101</td>
</tr>
<tr>
<td>1984–1985</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>1. Chloramphenicol and other drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Combinations of antibiotics and antipyretics, analgesics, analeptics, antihistamines, cardiotonic agents and immunoglobulins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Penicillins for topical and rectal use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Oxyphenisatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Combinations of psycho-pharmacological agents</td>
<td></td>
</tr>
<tr>
<td>Phase IV</td>
<td>1. Cefaloridine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Fixed-dose combinations of dipyrone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Fixed-dose combinations of cardiotonic agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>134</td>
<td>127&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Formulation altered, restricted to hospital use or indication changed.

<sup>b</sup> 110 had altered formulation, 7 restricted to hospital use only and 10 had changed indication.
provision of technical information to health professionals and in the performance of drug utilization studies by health authorities and research workers.

Since the utilization of drugs can be affected by the policies of a number of different departments or sections within the health authority, this sophisticated data bank continues to develop to meet the increasingly heterogeneous calls on its resources.

**Drug utilization and therapeutic auditing**

Spain has a population of about 38 million and the national health service covers over 98% of the population; the quantity of prescription data to be collected and processed is therefore enormous. Nevertheless, general descriptive information about the most frequently prescribed groups of drugs and the most frequently prescribed products within the health service enable the health authorities to keep an up-to-date check on prescribing (Table 3). The availability of such data allows particular attention to be paid to therapeutic groups or individual products whose level of utilization gives cause for concern. Since this information is often published, it can also stimulate further research by independent groups working at the national, regional or local level (6–8), which in turn provides the health authorities with valuable additional information about drug use in clinical practice.

**Drug information and education**

Several types of printed information on drugs are produced by the health authorities for prescribers, pharmacists and patients. They include: "transparency lists" offering comparative information on the clinical pharmacology and treatment costs of drugs within a particular therapeutic group; an information bulletin, which discusses the therapeutic use of drugs and often includes an article on drug utilization; a prescribing guide for primary health care workers, a series of quarterly booklets listing recently approved products, indicating their legal status (prescription-only medicine, hospital use, over the counter, etc.) and providing their data sheets; and finally a series of patient guides on the treatment of minor symptoms.

A major problem that remains to be tackled is the assessment of the effect such information has on prescribing habits and drug utilization patterns.

The pharmaceutical industry also provides information about its products and one of the functions of the health authorities is to monitor
Table 3. The most frequently prescribed therapeutic groups in Spain

<table>
<thead>
<tr>
<th>Therapeutic groups by frequency of prescription in 1981</th>
<th>Ranking in 1984</th>
<th>Ranking in 1987</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Expectorants</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>2. Broad-spectrum penicillins</td>
<td>(4)</td>
<td>(3)</td>
</tr>
<tr>
<td>3. Nonsteroidal anti-inflammatory drugs</td>
<td>(5)</td>
<td>(4)</td>
</tr>
<tr>
<td>4. Non-narcotic analgesics and antipyretics</td>
<td>(3)</td>
<td>(5)</td>
</tr>
<tr>
<td>5. Cerebral and peripheral vasodilators</td>
<td>(2)</td>
<td>(2)</td>
</tr>
<tr>
<td>6. Neuroleptics</td>
<td>(—)</td>
<td>(—)</td>
</tr>
<tr>
<td>7. Bronchodilators and anti-asthmatic drugs</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>8. Antacids and antiflatulents</td>
<td>(8)</td>
<td>(9)</td>
</tr>
<tr>
<td>9. Cough and cold remedies without anti-infectives</td>
<td>(10)</td>
<td>(10)</td>
</tr>
<tr>
<td>10. Penicillin and streptomycin combinations</td>
<td>(—)</td>
<td>(—)</td>
</tr>
<tr>
<td>— Tranquillizers</td>
<td>(7)</td>
<td>(7)</td>
</tr>
<tr>
<td>— Myocardial therapy</td>
<td>(9)</td>
<td>(8)</td>
</tr>
</tbody>
</table>

Source: Garcia Inesta (5).

the content and claims made in such promotional material. The most important source of information for prescribers in Spain is the Vademecum internacional (9), a compendium of data sheets produced by the pharmaceuticals industry on its products. Recently, the health authorities have undertaken to revise and approve the text of the data sheets of various drugs and products at the request of the companies; approved texts are distinguished in the Vademecum by the symbol of the health authorities. The number of companies requesting such revision is on the increase.

**Drug utilization and postmarketing surveillance**

As pointed out in Chapter 5, the value of adverse drug reaction data is greatly increased when incidence figures can be correlated with utilization data. In Spain, the Region of Catalonia has pioneered the monitoring of adverse drug reactions, and a number of valuable reports including utilization data have been published (10).

A recent nation-wide study in Spain (11) showed that the use of sex hormones in pregnant women was still high; collation of data from the
register of birth defects showed that a number of adverse effects were associated with the use of these drugs. Further investigation revealed that many of the women interviewed had used allylestrenol. This progestogen had been registered some years earlier for a range of indications including threatened abortion. Since revision of the licences for this therapeutic group was not due for some time, the availability of drug utilization data alerted the health authorities to the problem and helped in its resolution.

Conclusion
The Spanish health authorities’ data bank clearly has considerable potential, including its value for drug utilization studies. Up to the present, however, it has been used primarily for administrative and regulatory purposes. It is hoped that this situation will improve in the future with greater use of the data bank for scientific studies of drug use; such studies will in turn provide support for various of the activities carried out by health authorities.

Sweden
With the creation of a national health service that reimbursed the costs of prescription drugs after the Second World War, the Swedish health authorities began to show interest both in the drug bill and in the rational use of drugs. Databases were gradually developed that made it possible to analyse which drugs were being prescribed to whom, by whom, for which health problems and at what cost.

Work in this field in Sweden thus began unusually early and it became unusually comprehensive. As a consequence, the total sales of drugs can be followed over long periods for the country as a whole, as well as for counties, municipalities and single pharmacies. By means of prescription surveys, one can analyse the age and sex of purchasers of prescription drugs. From a systematic survey of diagnoses and therapy, the reasons why a drug is prescribed can be obtained, as can the specialty of the prescribing physician. In the county of Jämtland, individual purchases of prescription drugs have been recorded since 1970 in a sample that comprises one seventh of the population (16 000 people). This creates the possibility of estimating the incidence and prevalence of drug use in considerable detail (12).

Some examples can illustrate how the Swedish health authorities at the national level use the available drug utilization data.
Follow-up and feedback
Drug utilization data can be and are used to monitor the effects of various measures taken to modify existing patterns of drug use. Thus, if physicians are advised that a particular drug is the product of first (or last) choice, exact figures can be provided to show to what degree the recommendations have been followed. Sales figures can also be used to monitor whether warnings have been observed. Three examples can illustrate this.

Fenfluramine is an anorectic agent that should only be prescribed for cases of pronounced obesity where diet and other measures have failed. An analysis of the sales and prescription data showed a wider use than expected. This, together with adverse reaction reports of depression and other severe psychic reactions, led to a withdrawal of fenfluramine in 1987.

Piroxicam was introduced on the market in 1981. The sales grew rapidly, amounting, after about a year, to 6.8% of the sales of all analgesics with antipyrctic and antirheumatic effects. At the same time, the group of other analgesics showed only a minor corresponding decrease. The drug authorities objected to the marketing practices of the company responsible, after which sales gradually decreased.

In Sweden, various bulletins are issued by independent agencies, such as the Department of Drugs and the National Corporation of Pharmacies, to encourage the rational use of drugs. It is very difficult, however, to use drug utilization data to measure the effects of these information activities, since other information (such as that in the mass media) may be exerting an effect on prescribing habits at the same time. A rather old example from the late 1960s illustrates this problem (13). The Swedish Adverse Drug Reaction Committee had warned three times about the possible association of dipyrone and agranulocytosis, but it was not until the third time, when the warning also appeared in the mass media, that the message had any influence on the sales of the drug.

Drug utilization data as signals
In Sweden, the widespread use of hypnotics, sedatives and minor tranquillizers was questioned as early as 1970. Information to encourage stricter prescribing of these drugs was issued by the authorities, and the sales and prescription figures were subsequently followed.

It was found that the sales were relatively stable over the ensuing ten years but with a decrease in the prescribing of barbiturates. These
were shown to be prescribed almost four times as often in the most southerly county as in the most northerly. Prescription data showed that barbiturates were most often prescribed by elderly physicians for unspecified symptoms and insomnia. Almost half the prescriptions were for combined products; only 11% were for new patients. Such data indicated that barbiturate prescribing was an old and outdated therapeutic tradition. This, together with the risk of lethal intoxications, led the Swedish drug control authority to the conclusion that the benefits of barbiturates no longer outweighed their risks; questions put to the manufacturers resulted in the withdrawal of all oral barbiturates with the exception of phenobarbital.

Locally, the findings led to a detailed analysis of prescribing patterns for barbiturates and related drugs; it showed that, while most physicians were responsible for only a moderate number of prescriptions, some 10–15 had very high prescribing rates. The findings led to the holding of a scientific meeting at which indications for the prescribing of hypnotics, sedatives and minor tranquilizers were discussed; thereafter an information letter was sent by the local medical association to all physicians about the precautions to be taken in the prescribing of these drugs.

In this case, drug utilization data had not only pinpointed the problem but also rendered it possible to confirm the efficacy of the measures taken. During the following year, 1979, the sales figures for barbiturates and related drugs decreased from 82.9 to 78.0 DDD per 1000 inhabitants per day and in 1981 to 76.8. In parallel, the number of patients hospitalized because of the abuse of these drugs fell by 28.5%. The number of lethal barbiturate intoxications was also reduced (14).

The auditing process thus helped reduce both abuse and lethal intoxications. By 1988, however, sales figures had again risen to 80.2 DDD per 1000 inhabitants per day, which suggests the need for a renewed investigation into how hypnotics, sedatives and minor tranquilizers are being prescribed in this area.

**Evaluation of adverse reactions**

As discussed earlier in this section, adverse reaction reports should ideally be evaluated in the light of data on the extent of use of the drugs concerned, so that some indication of incidence can be obtained.

When reports on estrogens and endometrial cancer appeared in the medical press, the question was how many Swedish women might
be at risk. Sales data showed that sales had risen from 3.65 DDD per 1000 inhabitants per day in 1974 to 9.86 in 1976. From data in the prescription survey, it was estimated that about 80% of the drugs were being taken by women aged 45 years or older. On the assumption that each woman takes the drug for at least a year, the number of women exposed to the drug for at least a year in 1975 was estimated at 62 000, or 3.7% of the population. This figure is considerably lower than in the United States, where almost 50% of women at that time used estrogens during the menopause.

The decision was that the American findings, together with the Swedish data on utilization, did not warrant the withdrawal of the drugs. Instead, physicians were informed of the findings and a prospective follow-up of women on estrogens was initiated. In fact, the eventual conclusion was that the overall risk of cancer of the endometrium was not significantly increased by the use of estrogens and that the addition of progestogens could protect against the development of endometrial neoplasia after estrogen treatment (15).

Evaluation of cost
Drug utilization data can be used by health authorities in price negotiations. In Sweden, the data are used to estimate the size of a market, which in turn may affect the price regarded as acceptable.

Utilization data can also be helpful in making a choice between alternative ways of treating a disease, including drug therapy, surgical intervention, psychotherapy, lifestyle changes and so on. So far, however, very few comparisons have been made by the health authorities themselves. They have instead founded their decisions largely on data produced by researchers in health economics. Areas of interest have included the drug treatment of gastric ulcer (16) and hypertension (17).

Conclusions
The sources of information available on drug use vary from country to country. Some countries only have data on drug imports, others have data both on the sales and on the prescription level. As shown in the country case reports presented here, even crude data on sales can provide valuable information on which drugs are prescribed and the volume of drug consumption. It is especially important for countries with a limited health care budget to analyse the types of drug being
used and to make comparisons with lists of essential drugs such as those to be found in formularies or issued by WHO.

Drug utilization statistics are useful as signals that problems may exist, but they cannot indicate whether or not drugs are being used in a rational way. In-depth studies have to be carried out to see whether, for example, relatively high usage figures reflect the density of the physician population, the location of pharmacies, the age and cultural structure of the population, local therapeutic practices, or other logical or illogical influences. The results of these in-depth studies should then be available to all concerned, including prescribers, dispensing pharmacists, the drug industry and the health authority.

Drug utilization data have not been used to their full extent by health authorities. For the benefit of the patients and the taxpayers, auditing routines should be initiated at all levels, including that of the health authorities themselves. These auditing routines should not be regarded as a threat to prescribers; they can be extremely valuable to them in reflecting upon and seeking to improve their daily work.

Shaw (18) has presented guidelines on therapeutic audit that can be adapted to meet the needs of health authorities. The purpose should be educational and shown to be relevant to patient care. The method should be impartial, interesting, objective and repeatable. The resources spent should be economical, the methods as simple as possible, and the routines such as not to interfere with everyday work. Finally, the conduct and control of the audit should actively involve the people concerned with prescribing drugs, delivering them and, not least, using them.

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Drug utilization and the health professions

K.H. Kimbel

For the purposes of this chapter, I shall consider the health professions in the broad sense, including not only physicians and pharmacists but also dental surgeons, midwives, nurses and everyone else who in one way or another is involved in the prescribing, issuing and use of medicines.

There are a great many reasons why one should know what drugs are being used, why and how, whether by the community as a whole, particular subpopulations or individual patients. This chapter surveys some of the most important ones.

1. Monitoring the Quality of Drug Treatment

Has a certain drug improved or cured the condition for which it was given? Did all recipients or only a fraction benefit from the treatment? Was any benefit transient or lasting, and had it any effect on the quality of life?

All over the world, even in affluent, developed countries, the question arises whether the amount of money spent on drugs results in a proportional degree of improvement in public health and wellbeing. The ideal situation in which to study this question is where there is consensus about what constitutes optimal treatment for a particular condition; such a consensus at the global level is most likely to have been reached for infectious diseases or malignancies, but consensus is commonly attained on a broader range of issues at the national or regional level. Once it exists, differences in drug utilization between various areas, set alongside epidemiological data on the disorder itself, will indicate where there is substantial deviation from the agreed standard. If there are also reliable data on therapeutic response and
mortality, the consequences of using alternative therapeutic approaches can be profiled. In turn, all this information can be set alongside economic data (see below) to determine which of the therapeutic approaches in use are cost-effective.

Such issues often cannot be studied globally; an assessment of the most effective use of resources for combating a disease will often have to take into account racial, geographical, climatic and ethnic variables as well. Regional variations in body weight and in the proportion of slow metabolizers in the population may be relevant. On the other hand, some elements need to be rigidly standardized if any comparisons at all are to be made; one of these is the measuring unit for drug utilization, the defined daily dose (see Chapter 4). The same holds true for the determination of the endpoints of therapeutic success or failure, as well as for the definition of the classes and stages of disease, typically matters in which WHO has played a central role.

2. Comparing the Efficacy and Safety of a Drug or Treatment with Others in Comparable Populations

The selection of optimal therapy might seem, at first sight, to depend only on the results of rigidly controlled clinical trials in limited populations. Certainly these play a central role, but they are complemented by very large-scale data based on actual experience with the drug in the field, where surprises can be encountered. Particularly where evidence seems to be emerging that a drug has unexpected advantages in a particular situation or equally unexpected adverse effects, it will be vitally important to set these emergent data alongside information about the level of use of that drug. The conclusions may be as important to the good practice of medicine as they are to those engaged in research, manufacturing or regulation.

3. Examining the Effects of a Drug on the Natural Course of a Disease

The administration of a drug may leave a disease unchanged, limit its effects, or actually aggravate it. There are, too, still many countries—including a number of industrialized ones—whose drug regulatory systems are inadequate and where many products on sale contribute nothing to health care or actually do harm. Ridding the market of such
products can be a formidable task and may be entirely impossible, unless some hard data are available to measure the harm being done and the therapeutic opportunities being missed. A starting point can be provided by drug utilization data, since they will pinpoint the drugs that are most prominent in the field and deserve prime attention; even the “top 10” drugs in a market can include some that are useless or even harmful, as documented in the standard literature. Where this is the case, comparing usage figures with those in countries with high pharmacotherapeutic standards may be educative and helpful in correcting prescribing behaviour. Data on the sales of inefficacious and unsafe drugs in developing countries may also help to evaluate the ethical standards of the manufacturer involved. These issues are not exclusively of concern to regulatory agencies; particularly where those agencies are weak, the health professions themselves have the power to make important changes to the prescribing tradition, so as to increase benefit and decrease risk.

4. **Estimating Compliance**

Comparing the amount of drug prescribed with that actually taken may provide some surprises, as well as explaining some therapeutic failures. The issue of compliance is dealt with more fully in Chapter 6. Any health professional must be concerned, however, that only a limited proportion of the drugs he or she prescribes or dispenses are used correctly or even at all, and that some prescribed drugs are even passed on to and used by people for whom they were not intended. If used for medical purposes, data on drug utilization must be corrected for non-compliance by studies on patients, or with the assistance of relatives or nurses, or even by the determination of blood or urine levels. Such studies, and experiments to improve compliance, very clearly belong to the field of drug utilization and they can very well be undertaken at the local level, even within a single practice or dispensing area.

5. **Estimating the Proportion of Cases Actually Treated**

How effective is the attempt to ensure that all cases of a widespread or epidemic disease actually receive therapy? Sometimes the investigation of this matter will identify situations of both overtreatment and undertreatment.
Depending on the state of development of a country, a certain fraction of a population may not be reached by drug distribution services or appropriate medical care. Even in developed countries, patients may not be treated adequately with the drugs they need; not all diabetics and hypertensives are aware of their illness and their need for treatment. On the other hand, in certain developed countries many more patients receive benzodiazepines, laxatives or H₂ receptor antagonists than really need them. In instances such as this, a comparison of the epidemiology of disease with the utilization of drugs is likely to pinpoint either overuse or underuse.

6. Detecting as Early as Possible the Misuse or Abuse of Drugs

Drug abuse is a widespread, growing phenomenon, that appears to thrive irrespective of a country's political structure. Sometimes efforts to constrain the availability of illegal drugs seem to increase the pressure patients exert on physicians to prescribe medicaments that may be taken as surrogates for drugs of abuse. Drug abusers and addicts are, for that matter, diligent at discovering the euphorogenic or hallucinogenic effects of new drugs or drug combinations, often before they are known to all physicians. Drug utilization studies can therefore be invaluable as early indicators of drug abuse. Drug utilization figures on controlled substances such as opioids are already available from the authorities; publication in the professional media would be helpful so that the extent of the problem and current trends could be widely recognized.

In the broad sense, drug abuse also extends to the use of anabolic steroids or other agents to promote strength or physical development in adults. A difficulty here is to distinguish licit from illicit use, if the former still exists, since the remaining indications for anabolic steroids are few and controversial.

7. Enabling Physicians to Compare Their Prescribing with That of Their Colleagues

The first drug utilization statistics in western Germany, such as those published by Westermann & Greiser over 20 years ago, elicited profound reactions from general practitioners and internists, the
very professionals who were prescribing the lion’s share of drugs to ambulatory patients. The fact that cardiac glycosides figured among the most prescribed drugs was debated widely in meetings and in the literature. The debate was an early example of the fact that physicians can profit from knowledge of the prescribing habits of their colleagues and the profession as a whole, and that they are often willing to do so. Naturally there were dissonant voices; some defended the high level of prescribing, while others took the figures as a basis for incriminating physicians whose prescribing habits deviated from their own.

Sometimes even quite simple and global information can be instructive. A recent survey among general practitioners and internists in a large industrial city in Germany revealed that general practitioners prescribe an average of 552 and internists 585 different drug preparations. These figures alone give food for thought; it seems highly unlikely that a physician is sufficiently well acquainted with so many different drugs to be capable of using them logically. The fact that physicians may also quite rapidly change their selection of preferred drugs is even more worrying; most of the 81 physicians surveyed in the study had, within a short period, replaced 20–39% of the 40 drugs they most often prescribed by other drugs, thus further eroding their information basis.

Despite some criticism of the opening of prescribing records in this way, such data are most commonly regarded by health professionals as instructive, and as a reason to review their own prescribing critically. Other aspects of this matter are considered under the next point.

8. Self-auditing

Without some methodical attempt to analyse their own prescribing, health professionals may have quite a mistaken idea of how they are actually practising drug therapy.

The corollary of what has been said above – about a physician’s insight into what his or her colleagues are prescribing – is that the physician must also have an overview of what he or she is prescribing, if any logical comparison is to be possible. That might appear self-evident, yet without a systematic collection of data physicians may have an entirely false impression about their own prescribing patterns. The reaction of physicians all over the world when confronted with their own prescribing figures is almost uniformly one of astonishment:
“Did I really do that? That cannot be!”. The realization of the facts can motivate them strongly to seek expert advice on improving their own prescribing, or to discuss it with colleagues working in a similar practice. Such practices can be further encouraged if medical students are taught to regard self-audit as an integral and essential part of a medical career.

In some instances, the physicians’ own records will provide the data they need; in many other instances, a pharmacy with a computerized data collection can be helpful; sometimes the data will emerge from a centralized sickness fund system. Some organizations, such as the Sick Fund Physicians Associations in Germany, provide their members with computer printouts of all the drugs they have prescribed in the preceding quarter, broken down by groups of drug and individual patients as well as by numbers of prescriptions and costs.

For the future, it would be desirable to ensure that drugs listed on prescriptions are at some stage allotted a code number (such as the ATC code, to be added at the pharmacy in machine readable form). This would facilitate subsequent computer analysis of the data.

Physicians who decide to take their own prescribing practices in hand and improve them can tackle the problem in various ways. Some physicians, liberally supplied with commercial samples, simply put them on a table and sort them into positive and negative groups, as a means of choosing the drugs they will continue to use; others systematically draw up a “personal positive list” and revise it at intervals.

9. Developing and Assessing Corrective Measures

Where drug utilization does not clearly serve the best interests of the patient or public, means need to be identified and tested to improve the situation.

The discovery that cardiac glycosides were being overprescribed in western Germany led to a dramatic fall in prescriptions over the next few years, even before newer products for the treatment of heart failure had become available. There was an analogous decline in the prescription of benzodiazepine sedatives (though not of hypnotics) when the dependence problem became known to general practitioners. Drug utilization studies had assisted in identifying both problems and they were indispensable in measuring the extent to which they had been solved.

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10. Assisting the Educator

People giving professional education in this field need to know how to set their priorities and to determine the success of their efforts to influence prescribing behaviour.

The relatively short life of drugs means that what the young physician learns about drugs at medical school becomes partially obsolete within a few years. Teaching to ensure better prescribing must therefore take place at both the undergraduate and postgraduate levels. The former will equip physicians with basic and applied pharmacological knowledge and with the ability to take logical decisions; the latter will guide them in dealing with a changing therapeutic world. One must interpret a term such as “postgraduate education” broadly; it comprises, in fact, not merely being taught in an organized fashion at courses, but also acquiring information and advice from a wide range of journals, bulletins and other media, including many that seek to maintain their independence and attain objectivity. Everyone involved in providing such information is an educator; all need data from drug utilization studies to identify areas of therapeutic uncertainty and error, and to assess the impact of their own work.

11. Controlling the Economics of Drug Supply

The cost factor in drug use is dealt with in detail in Chapter 7, primarily as it concerns national administrations. It is also a matter, however, that must concern the health professional.

To consider first the pharmacist, maintaining a sufficient supply of drugs requires considerable financial investment. If excessive stocks are kept, however, money will be wasted, a loss that will ultimately be borne by the consumer; in addition, of course, excessive stocks increase the risk that many drugs will exceed their shelf-life and have to be discarded. A knowledge of expected drug utilization is a sound basis for maintaining realistic inventories at both the wholesale and retail level.

Physicians are likely to find themselves under increasing pressure to prescribe economically, but the evidence put before them as to what actually constitutes economical prescribing is not always consistent. Drug treatment is often claimed to be the most economical way to treat disease. This may be true in a limited area, where long-term physical or psychological therapy or costly surgery seems the only alternative.
For other conditions, however, realistic alternatives can involve less expense and risk, and be to the patient’s advantage; examples include the dietary treatment or prophylaxis of hypercholesterolaemia, early diabetes, mild hypertension and constipation. Assessing the relative merits of those approaches is a medical and nutritional matter; assessing the relative costs is a job for the health economist; but in order to evaluate and understand the overall scene, one will need to call upon both the epidemiologist and the student of drug utilization.

At the hospital level, cost considerations may play a central role, sometimes even crucial to a hospital’s survival. Again it becomes important to know what is being prescribed, for which condition, with what justification, and what it costs. Many a hospital has found that an audit of its use of drugs provides the impetus for drawing up a formulary suited to the needs of its staff and patient population.

Fortunately, progress in drug research is now accelerating after years of stagnation. To make the results available to all who need them, irrespective of race or nationality, funds must be wisely apportioned between the new and the old drugs. Drug utilization studies can make a most important contribution to that goal, as to so many others.
Consumers as instigators and users of drug utilization research

A. Herxheimer

People who take medicines often know little about them and how they should be used. On the contrary, they are liable to have mistaken ideas or beliefs that lead them to use the medicines in ways that make them less effective or more hazardous than they could be. Popular beliefs and practices are based on folk traditions, including various traditional systems of medicine, on medical dogmas of past decades, on what doctors and other health experts say, and on the commercial promotion of medicines and other health products. Anyone who wants to improve the way medicines are used in the community must take account of the prevailing beliefs and practices. Their nature, strength and prevalence determine many aspects of drug utilization.

If beliefs are to be changed, one must discover what they are, where they come from and how they are maintained. Which individuals in a society or in a family act as teachers and disseminators of knowledge about medicines? How can they be involved in attempts to improve the way medicines are used in the community?

Whenever it is proposed to give patients information about medicines, a basic issue is whether the information will help or hinder treatment.

On the one hand, patients should, as far as possible, take responsibility for carrying out the treatment correctly, and to do this they need certain information. Furthermore, most would argue that patients have a right to know what is being or will be done to them, up to the limit of their understanding. On the other hand, too much information, especially in technical language, clearly risks confusing people and can be counterproductive. Lists of possible side effects can frighten patients and put them off taking a drug they need. These problems are not arguments against providing information, however, merely
against giving it in a certain way. They can be avoided by carefully selecting and presenting the items of information and explaining them to patients.

**Consumers and Patients in Drug Utilization Research**

Although patients are also consumers, the two concepts can usefully be distinguished because most consumers at any one time are not patients. Consumers need initiative and energy to work on general issues involving drug utilization, and tend to have enough of either only when they are in good health; they usually work through a consumer organization. Patients, on the other hand, are apt to be deeply and intimately concerned with their illness, and may devote much of their energy to fighting it, not only for themselves but also for fellow sufferers. This has led to the establishment of many disease-centred patient organizations, some of them very active and influential, with excellent back-up from medical experts. Examples in the United Kingdom are the British Diabetic Association, the Parkinson’s Disease Society and the Cystic Fibrosis Society.

Van der Geest & Hardon (1) have reviewed the methods (discussed in Chapter 5) that can be used to conduct field research on the use of western medicines in developing countries. They point out that development aid and consumer organizations, which involve solely consumers in their work, may be better able than other agencies both to carry out some types of drug utilization research and to apply the results directly in the community from which they derive. Such research especially includes interviews, structured and unstructured, of people in their homes, surveys of medicines kept in the home, the use of illness and medication diaries, and group discussions. Local action-oriented research may have important effects in a community that do not become known outside it, and those who undertake it often need encouragement to publish the results in scientific journals.

Consumer groups also have an interest in drug utilization research centred on the providers of medicines, such as physicians, pharmacists and drug sellers, and their prescribing and drug-selling behaviour. The results are used to inform and warn consumers what to expect in their encounters with providers of medicines, and to help them achieve more satisfactory interactions with them. They are even more useful for persuading the media, professional associations (of pharmacists, for example), industry, government authorities and politicians that specific improvements are needed.
Drug utilization research centred on a particular disease or health problem has not been prominent in the work done by consumers. Consumer work does include, however, surveys of members of self-help groups active in specific fields, such as the Multiple Sclerosis Society (2) and the British Diabetic Association (3), and studies by campaigning groups, such as the Association for Improvements in the Maternity Services and the National Association for the Welfare of Children in Hospital.

The claims manufacturers make and the information they supply about their drugs have an important bearing on the drugs' manner of use. Studies of the claims made for products and of the information given to prescribers and users are not strictly drug utilization research, but they complement it because they are concerned with one of the most important factors influencing utilization. Many studies of this kind have been done in the last 15 years. Among the first were analyses made by the International Organization of Consumers’ Unions of the indications and warnings given in various countries for chloramphenicol (4) and clioquinol (5). Since then a great deal of work has been done on a wide range of drugs, for example, by Silverman (6), Medawar & Freese (7), BUKO (8), Chetley (9) and Chetley & Gilbert (10), most of whom are participants in the Health Action International network. Such studies continue to contribute greatly to higher standards and greater international uniformity in the marketing of medicines and in the information provided about them.

Another type of drug utilization research deals with the development and use of drug formularies. Most work of this kind has been done by pharmacists and physicians, but a recent survey of hospital formularies in the United Kingdom (11) was undertaken by Social Audit, an organization associated with the consumer movement.

Consumers as Users of Drug Utilization Research

Clearly only a relatively small portion of the drug utilization research undertaken by consumer organizations or by others is used directly to influence the utilization of drugs by consumers themselves. Since health professionals, government agencies and industry, rather than consumers, very largely determine patterns of drug utilization, consumer organizations tend to concentrate on trying to influence these groups, by lobbying them and by public campaigning. Such lobbying and campaigning depends heavily on drug utilization data, particularly
data obtained directly from patients themselves. One dramatic example is the *That's life* survey on tranquillisers (12), conducted during preparations for a television programme on benzodiazepine dependence, which evoked a vast response: over 3000 viewers wrote in recounting their own experiences. With the cooperation of MIND, the National Association for Mental Health, the programme undertook a survey of viewers who had been prescribed these drugs: 2150 completed a detailed questionnaire. Another example is the British Diabetic Association's survey (3) of its members' experiences with the new human insulin preparations. The results give valuable information on the problems that arise with these preparations, which should enable physicians, patients and manufacturers to overcome or minimize them.

Sales and prescription data provide the best information on the importance of different drugs and are therefore valuable in identifying priorities for campaigning. Unfortunately, such data are unavailable or kept secret in many countries. Quantitative data on adverse reactions are also important.

When consumers and their advocates use drug utilization data, they must be aware that their correct interpretation requires an understanding of their limitations. Drug utilization data can hardly ever be taken at face value; they must be considered in relation to the prevalence of the relevant disease or health problem, to the special subpopulations using the drug, and to the structure of the health care system. For instance, the use of oral contraceptives should not be related to the population as a whole, but only to the subpopulation of women in the reproductive age groups exposed to the risk of pregnancy. The interpretation of quantitative data on adverse reactions is even more complicated. Estimates of their incidence obviously depend on the denominator, the number of people exposed to the drug and the detection and reporting rate for the particular reaction. For these reasons, it is highly desirable for consumers to have access to independent scientists who are experienced in the interpretation of pharmacoepidemiological data.

References


Drug utilization and the teaching of rational drug use

J.R. Laporte & M.L. Orme

If the results of teaching pharmacology had to be measured by the quality of drug use, the teachers' performance could easily be qualified as a failure. In many places in the world, the conditions surrounding the provision of health care are clearly an invitation to irrational use. In some countries, drug registration policy has not been based on the principles of rational scientific evaluation. It has permitted or tolerated the entry into the market of many drugs that must be characterized as unnecessary or confusing, or sometimes frankly illogical, ineffective and useless. As a consequence, the supply of pharmaceuticals may be an incitement to the misuse of drugs. Drug information can be monopolized by pharmaceuticals firms and, even for drugs that have some merit, this information is often biased and tendentious; it tends to induce careless prescribing and at worst almost a spinal reflex ("Symptom A calls for drug B..."), rather than rational prescribing based on sound advice and a careful weighing up of the alternatives.

The identification of these negative influences does not, however, exonerate teachers from responsibility; it should do exactly the opposite. Do we prepare our students to cope with these challenges adequately and efficiently? If they are able to identify so many "non-scientific non-pharmacological" factors that influence drug utilization, why do they not face them frankly in the undergraduate teaching of future health professionals?

This chapter provides some preliminary reflections on the teaching of the health professionals who play a central role in drug utilization. It focuses in particular on teaching the medical undergraduate as a future prescriber, but much of what is said applies directly to the teaching of pharmacology to future pharmacists and nursing staff, as well.
The Academic World and Clinical Practice

The academic world of pharmacology stands, in some respects, at a distance from the real world of clinical practice; some of the differences between the two are highlighted in Table 1.

First, there is a remarkable difference in the words used. The names of drugs provide an example. When teaching the use of drugs one must refer to them by their generic names; this is the only possible approach if the student is to learn pharmacology rather than commerce, but one always has to bear in mind that once in practice the new physician will be confronted with a quite different nomenclature. One drug may have half a dozen commercial names, each endowed by publicity with its own image; it will sometimes be difficult for the physician to penetrate to the true identity and nature of the drug on offer. To a lesser extent, the problem of differing nomenclature will confront new physicians in other areas, as well; terms with which they believe they had become familiar—diseases and symptoms, plasma concentrations, half-life, first choice treatment, efficacy, potency, unwanted effects—may prove to have a subtly different connotation when they appear in the promotional material distributed by pharmaceuticals firms, and the prescribers themselves may begin to understand them differently.

Second, newly qualified physicians will also encounter some statistics they did not expect; the basic textbooks of pharmacology will have familiarized them with several hundred pharmacological compounds; a prescribing textbook may extend to some 1500; yet, in a country such as Spain, the physician will have to wrestle with a market in which (at the time of writing) 2,450 different active principles are available, presented under 5,500 trade names and in the form of over 14,000 preparations. The situation may be less extreme in some other countries, but the phenomenon—and the confusion it causes—is almost universal.

Third, physicians will discover that the matters considered important when they learned pharmacology are somewhat different from those now brought emphatically to their attention. Whatever they learnt about chemical structure or mechanisms of action will lie fallow; instead they will be pressed to consider indications, dosages and the supposed advantages of one product over another.

In this discussion, then, a number of issues can already be identified where undergraduate teaching needs to be better adapted to the
Table 1. Drugs in the academic world and in clinical practice

<table>
<thead>
<tr>
<th>Elements of drug utilization</th>
<th>In teaching</th>
<th>In practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug description</td>
<td>Generic names</td>
<td>Trade names</td>
</tr>
<tr>
<td>Drug availability and form</td>
<td>&lt; 100 drugs</td>
<td>1000–10 000 pharmaceutical products</td>
</tr>
<tr>
<td>Important drug characteristics</td>
<td>Chemical structure, mechanisms of action (half-life, volume of distribution, etc.)</td>
<td>Available preparations, clinical effects (mostly symptomatic), duration and pattern of effects</td>
</tr>
<tr>
<td>Choice of drugs</td>
<td>Few guidelines, but stress on diagnosis and knowledge of pharmacology</td>
<td>Temptation to prescribe symptomatically or by spinal reflex</td>
</tr>
<tr>
<td>Approach to drug therapy</td>
<td>From drugs to problems (drug-oriented thinking)</td>
<td>From problems to drugs, which may or may not be useful for their resolution (problem-oriented thinking)</td>
</tr>
</tbody>
</table>

world outside the university. The university should not surrender to it, but it should do a great deal more to prepare future health professionals to face it critically, to understand the language they will encounter, and to make rational decisions in what are sometimes irrational situations. To take a simple example, students of pharmacology will no doubt have learnt the meaning of the word antitussive and they may have encountered the term expectorant, but are they prepared to face syrups that are claimed to be antitussive expectorants and are they capable of discerning that the two concepts are incompatible and the mixture therefore irrational? As pointed out in Chapter 9, the basic task of undergraduate teaching in this field is to equip the student with a broad understanding of pharmacology, pharmacodynamics and pharmacokinetics, supplemented by a knowledge of the principal agents used in medicine; it is vital, however, that this teaching be complemented by other elements, including an understanding of the links between these
matters and the commercial scene. That may mean a careful reconsideration of the teaching more traditionally given; does one need to devote so much attention to chemistry, to biochemical receptors, and to supposed mechanisms of action that may be no more than transient hypotheses?

A separate but equally important problem relates to the divorce one commonly encounters between the basic teaching of pharmacology and the reality of the sick patient. Despite its scientific foundation, the teaching of pharmacology is often marked by an unwillingness or even an inability to relate drug properties to clinical disease. Pharmacology teaching programmes are thus more drug-oriented than problem-oriented. In the later, clinical phases of medical training, a complementary problem arises: the undergraduate is taught the therapeutics of the major diseases by academic clinicians who are more interested in the rationality of differential diagnosis than in the rationality of therapy. It is little wonder that, provided only with this unstable foundation on which to build their future prescribing habits, most health professionals ultimately learn more about new drugs (or new uses of old drugs) from the so-called drug detailman or pharmaceuticals representative than from their rightful teachers.

In this situation, therefore, teaching the practical aspects of drug use becomes a pressing need. The efficacy of drugs in the field depends on what prescribers actually do, and currently this may have little connection with what they were taught. The real prescribing conditions in the country where the physician is most likely to work must be taken into consideration when designing a teaching programme.

The central problem is to pinpoint the knowledge and skills required for rational drug prescribing and to decide which elements can be set aside. The pharmacologist should know whether insulin contains one or two disulphide bridges, or captopril has a thiol group, but for the clinician it is more important to know why a drug has to be administered, at what dose, by which route, how often and for how long. Mitchell compares the learning process of a medical student in pharmacology with that of the future car driver (1):

...we would not begin by reading a book on the structural formula of petrol and how to make it, or on the hysteresis curves of the tyres under stress, the metallurgy of the body, or the air flow characteristics of the venturi in the carburettor. We would simply accept that if you pressed the accelerator the engine would deliver more power and we would then want to be told how to use that power to make us safely mobile.
Once we were competent we would realise that accidents invariably occur because drivers don’t foresee, don’t judge, or are influenced by alcohol, rather than because they don’t know the definition of brake-horse-power or whether their engine has twin overhead camshafts.

And – paraphrasing Sir Richard Doll – Mitchell concludes that (1): “...such books are for botanists and not gardeners, for astronomers not navigators, and for car designers not drivers”.

Elements for a Teaching Strategy on the Rational Use of Drugs

There is no simple solution to the prescribing conundrum raised by the vast and constantly shifting spectrum of drugs on the market. It has been suggested that a well trained clinician may expect to know in some detail the pharmacology of 25–35 products or perhaps even of 50. Clearly, the solution is not to extend that list interminably in an effort to teach the student about the plethora of “me-too” drugs on the market (2, 3). The only possible approach is to base the teaching of pharmacology and therapeutics on the selection of drugs. Certainly, examples of useless, ineffective and unacceptable drugs should be clearly and explicitly quoted, and physicians taught to recognize their like when they encounter them in practice; this will assist the future prescriber to appreciate the difference between trying to manage clinical problems and merely looking for drug indications. Beyond that, however, teaching must concentrate on essentials: clinical and epidemiological problems and challenges.

If one is to teach the therapeutic strategies needed to approach common and dominant clinical problems, an undergraduate teaching programme in clinical pharmacology should cover some key areas that are not handled by other clinical disciplines. These will include reading and interpreting clinical trial reports, understanding the potential therapeutic implications of pharmacokinetic profiles, appreciating the mechanisms, frequency, severity and diagnosis of the undesirable effects of drugs, and knowing something of the legislative, economic and social aspects of the use of medicines. Teaching about specific drugs will concentrate on major drugs, on the comparative profiles of some similar drugs, and above all on diagnostic and therapeutic strategies for common problems. Herxheimer has suggested the systematic use of a list of questions that students can put to themselves to test their real understanding of an individual drug (Table 2).
Table 2. Checklist of questions used in training medical students in the use of drugs

To all clinical students

QUESTIONS TO ASK YOURSELF ABOUT DRUGS

One of your main chances to learn about drugs occurs while you are doing clinical work. The questions below will help you to learn more systematically from this experience. Ask yourself these questions to assess your knowledge. If you cannot answer them for yourself, discuss them with those who are treating the patient.

Look at the treatment sheet at the end of the patient’s bed or the outpatient prescription form. Some of the drug names may be unfamiliar. You will need to find out about these.

1. Name For each drug listed, what is the approved or generic name?
2. Class To what therapeutic or chemical class does each drug belong (e.g. diuretic, phenothiazine)?
3. Aim What aim is to be achieved with each drug? What disorder of function is to be corrected, or what symptom relieved?
4. Observations What observations can be made to judge whether the aim has been achieved? When should they be made and by whom?
5. Route and dosage By what route, in what dose, and at what intervals is each drug to be given, and why? In what form(s) does each drug come?
6. Alternatives What other remedies might have been chosen instead if these drugs? Is this drug a good choice (efficacy, safety, cost)?
7. Duration How long should treatment go on, and when and how could a decision be made to stop it?
8. Elimination How is the drug eliminated? Will the patient’s illness change the usual pattern of distribution and effects of the drug?
9. Unwanted effects What unwanted effects may this drug have? Are they acceptable? What is their approximate frequency?
10. Interactions Are there any other drugs that should be avoided while the patient is receiving this treatment? If yes, which are they and why should they be avoided?
11. Patient’s ideas What does the patient believe about the drug? What has he/she been told about it? And what has he/she remembered? Does he/she need additional information?

Source: Herxheimer (4).
A number of general goals should be central when one plans or restructures the teaching of clinical pharmacology to medical undergraduates.

1. At the end of their training, physicians should be able to select the adequate drug and regimen for each patient in most general practice situations. To achieve this goal, they should be able (5):

(a) to read and evaluate scientific literature on new drugs and therapeutic strategies;

(b) to take a complete and reliable drug history of the patient;

(c) to identify physiological, pathological and social factors that may influence the selection of the drug, its administration regimen and the pharmaceutical form used;

(d) to identify diagnostic tools and skills that are needed for the prescription of each drug;

(e) to inform and instruct the patient on how drugs should be taken, on the expected duration of the treatment, on the expected benefits, on the most common adverse effects and how to deal with them, as well as on the non-pharmacological measures employed;

(f) to write a prescription.

2. At the end of their training, physicians should be able to evaluate the beneficial and adverse effects of drugs. To achieve this goal, they should:

(a) know the expected time course of drug effects in relation to the pharmacokinetic profile;

(b) be able to diagnose the adverse effects of drugs and to report them when they are serious or unexpected.

The extent to which reforms in the teaching of medical students are enabling those goals to be attained is not clear. Tables can be drawn up indicating the number of hours devoted, in different universities and countries, to teaching on drugs at the basic and clinical levels, but these figures themselves (many of which are to be found in a WHO study of clinical pharmacology described below (6)) give no insight into the quality and relevance of the instruction being given.
Clearly, however, a small nucleus of universities exists where valiant efforts are being made to reorient teaching so as to serve the future physician better.

**Progress in the Teaching of Clinical Pharmacology**

The term clinical pharmacology has already been used in this chapter, to describe the clinically relevant teaching on drug matters that the undergraduate needs to receive. One must, however, also pause briefly to consider the development and teaching of clinical pharmacology itself as a specialty in medicine; increasingly it has been realized that such specialists are needed to support the rational use of drugs in society. The clinical pharmacologist can function as a teacher, a regulator or a researcher, but also as a practising specialist to whom other physicians can refer patients who are experiencing what is essentially a drug problem.

Under the auspices of WHO, a clinical pharmacology team has been examining the teaching of clinical pharmacology in European countries (6). Suffice it to say here that the picture is far from rosy and that most European countries – with a few notable exceptions – have very few qualified clinical pharmacologists and almost no specialized training in the subject. The prospects for improvement in the immediate future do not seem bright.

**Drug Utilization and the University**

The essential relevance of the university to drug utilization is that medical teaching holds an important key to the future manner of drug use. Where drug utilization patterns leave much to be desired – as they commonly do – it is all too easy to blame the pernicious influences that lure the physician into improper prescribing. Such influences are there, but they are effective only because the average physician today is so inadequately equipped to resist them. A physician properly trained to understand the drug scene and to make prescribing decisions rationally will prescribe well despite pressures to the contrary. The challenge facing the universities is to achieve that ideal. To do so, university teachers themselves must understand the drug scene and the way drugs are prescribed today. Utilization studies, in which the medical faculties and teaching hospitals can play an exemplary role, will provide the key to that understanding.
References

Drug utilization studies: their transferability between industrialized and developing countries

D. Lee, K. Balasubramaniam & H.M. Ali

Drug utilization studies, like drugs themselves and other medical technologies, have as a rule been developed and come first to fruition in the more advanced industrialized countries. The broad spectrum of methods used and the parallel development of the major lines of clinical/epidemiological, social and economic drug utilization research have been reviewed in previous chapters.

The contributions of drug utilization studies to the implementation of national health policies have similarly been felt first in the industrialized countries. Developing countries, by contrast, have a greater need for drug utilization research as a tool to measure the effectiveness and efficiency of drug use; one must realize that in these countries, despite an estimated 60% of the total health budget being spent on drugs, large segments of the population still do not have access to efficacious, safe and inexpensive drugs (1-3).

The problems of and possible approaches to conducting drug utilization studies in developing countries cannot be examined without some understanding of the technological, social, cultural and economic facets of these countries. The multiplicity of factors affecting drug consumption are summarized in Fig. 1. Legislation, regulatory actions, quality control and action-oriented drug utilization studies are other potential determinants of drug use.
Fig. 1. Factors affecting drug consumption

Population size:
- demographic structure
- occupational structure
- nutritional status
- income level
- income distribution

Health services:
- number and type of health facilities
- number and type of health personnel

Geographic factors

Morbidity pattern

Availability and use of health care facilities

Number and type of cases seen

Diagnosis by health worker

Prescription patterns

Marketing practices

Volumes and mix of drugs prescribed

Price

Availability

Prescription filled

Patient compliance

Volume and mix of unprescribed drugs consumed

Volume and mix of prescribed drugs consumed

Consumer's perceptions of health

Source: adapted from Col & O'Connor (4).
Developing Countries: Some Relevant Characteristics

Developing countries differ from industrialized countries in a number of general respects as well as in matters relating directly to health and drugs (Table 1).

Socioeconomic, demographic and health-related indicators

Developing countries constitute a wide spectrum of nations at different stages of development, various stages often being evident within a given nation. Most of these countries are small and poor, over 50% of them have fewer than three million people each and over 50% have a gross national product (GNP) per head of less than US $1000 (Table 2).

Important differences may be observed in selected health-related indicators between industrialized countries and those developing countries with low or middle incomes (Table 3). Despite ethnic and social differences among and within these countries, however, the problems related to health and drugs are similar in nature while varying in magnitude (8).

Health needs

The priority health needs in developing countries are those related to poverty: malnutrition and infectious diseases (diarrhoeal and acute respiratory infections and other preventable diseases). Many of the infectious diseases may be treated with effective and affordable drugs or prevented by immunization, while others are endemic and not yet controllable. Even within individual developing countries, a bimodal distribution in health problems may occur – one form being characteristic of the rural poor, the majority of the population (infectious diseases, malnutrition, etc.), and the other characteristic of the privileged urban minority (cancer and cardiovascular and other chronic diseases) (7). This situation contributes significantly to conflict and confusion in the allocation of limited resources.

The real need (as opposed to demand) for drugs as effective remedies is rarely, if ever, assessed in developing countries. This deficiency is related partly to the organization and functioning of the health care delivery infrastructure and partly to the lack of financial and technical resources (9). The health information system may be nonexistent in terms of health statistics and surveillance. Quantitative data from existing health information systems may be of questionable quality, although such data may still be of some use in setting priorities.
Table 1. Major differences between developing countries and industrialized countries as regards the health and drug scene

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Developing countries</th>
<th>Advanced industrialized countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross national product</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Expenditure on drugs</td>
<td>40–60% of total health budget</td>
<td>8–20% of total health budget</td>
</tr>
<tr>
<td>Health needs</td>
<td>Acute (diarrhoea, respiratory, etc.) and chronic (tuberculosis, malaria, etc.) infections</td>
<td>Chronic diseases (cardiovascular diseases, cancer, rheumatic diseases)</td>
</tr>
<tr>
<td>Alternative systems of health care (traditional medicine)</td>
<td>Important in many countries</td>
<td>Less significant</td>
</tr>
<tr>
<td>Health delivery systems</td>
<td>Concentrated in urban areas</td>
<td>Almost universally accessible Well organized</td>
</tr>
<tr>
<td>Priority in drug policy</td>
<td>Availability of essential drugs</td>
<td>Drug quality assurance (efficacy, safety and pharmaceutical quality)</td>
</tr>
<tr>
<td>Drug registration</td>
<td>Weak regulatory authority</td>
<td>Stronger regulatory authority</td>
</tr>
<tr>
<td>Drug availability</td>
<td>Unreliable</td>
<td>Consistent</td>
</tr>
<tr>
<td></td>
<td>Great dependence on imports</td>
<td>Significant drug development/ production</td>
</tr>
<tr>
<td></td>
<td>Inefficient drug distribution network</td>
<td>Efficient drug distribution network</td>
</tr>
<tr>
<td></td>
<td>Most drugs obtainable without a prescription</td>
<td>Most drugs not obtainable without a prescription</td>
</tr>
</tbody>
</table>
Table 2. 157 developing countries grouped according to their populations and GNP per head, 1979

<table>
<thead>
<tr>
<th>Population (millions)</th>
<th>No. of countries</th>
<th>No. of countries with GNP (US $) per head of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.005</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>0.005– 0.05</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>0.05 – 0.1</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>0.1 – 0.5</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>1.0 – 3.0</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>3.0 – 5.0</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>5.0 – 10.0</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>10.0 – 20.0</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>20.0 – 50.0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>50.0 – 100.0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>100.0 – 200.0</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>200.0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>15</td>
</tr>
</tbody>
</table>

### Table 3. Health-related indicators in countries with different income levels

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Year</th>
<th>Developing countries</th>
<th></th>
<th>Industrialized countries&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low-income&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Middle-income&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Gross national product per head (US $)</td>
<td>1979</td>
<td>240</td>
<td>1420</td>
<td>9940</td>
</tr>
<tr>
<td>Crude birth rate (births/1000 population)</td>
<td>1979</td>
<td>42</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Crude death rate (deaths/1000 population)</td>
<td>1979</td>
<td>16</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Life expectancy at birth (years)</td>
<td>1979</td>
<td>51</td>
<td>61</td>
<td>74</td>
</tr>
<tr>
<td>Infant mortality rate (deaths/1000 live births)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1978</td>
<td>49 – 237</td>
<td>12 – 157</td>
<td>13</td>
</tr>
<tr>
<td>Child mortality rate (deaths/1000 children 1–4 years old)</td>
<td>1979</td>
<td>18</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Population with access to safe water (%)</td>
<td>1975</td>
<td>25</td>
<td>58</td>
<td>N.A.&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Daily calorie supply per head (% of requirement)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1977</td>
<td>96</td>
<td>109</td>
<td>131</td>
</tr>
<tr>
<td>Adult literacy rate (%)</td>
<td>1976</td>
<td>43</td>
<td>72</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Thirty-four countries with an income per head of US $370 or less in 1979 (China and India are excluded from the low-income groups in this table).

<sup>b</sup> Sixty countries with an income per head of more than US $370 in 1979.

<sup>c</sup> Eighteen countries.

<sup>d</sup> Weighted averages: figures in parentheses denote the sample range.

<sup>e</sup> Data not available, but assumed to be close to 100%.

<sup>f</sup> Requirements based on calories needed to sustain a person at normal levels of activity and health, taking into account age and sex distributions, average body weights, and environmental temperatures, as estimated by the Food and Agriculture Organization of the United Nations.

**Source:** Evans et al. (7).
Table 4. Traditional systems of medicine in developing countries

<table>
<thead>
<tr>
<th>System</th>
<th>Countries where practised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayurveda</td>
<td>India, Nepal, Sri Lanka</td>
</tr>
<tr>
<td>Siddha</td>
<td>Southern parts of India</td>
</tr>
<tr>
<td>Unani</td>
<td>Bangladesh, India, Indonesia, Pakistan, Middle-East countries</td>
</tr>
<tr>
<td>Chinese</td>
<td>China</td>
</tr>
<tr>
<td>Herbal folklore/tribal</td>
<td>All over the world</td>
</tr>
<tr>
<td>Homoeopathy</td>
<td>All over the world</td>
</tr>
</tbody>
</table>

*Source: Sharma (12).*

Health care systems

Public and private health care systems coexist in most countries, but their coverage varies extensively. Many developing countries have alternative systems of health care (Table 4) and, in some, they are the main source of health care for the population (10–12). For example, in India only 20–25% of the population have regular access to western medicines. In certain countries of Africa, 70% of the population use traditional medicine. Large minorities in some countries may prefer traditional care to care from health personnel, partly because of the health system’s lack of credibility (through lack of drugs, etc.). Traditional medicine has an impact on the western model of medical care; one effect may be a lack of awareness of the potential risk of western drugs, impeding efforts to monitor adverse drug reactions and affecting compliance in both short- and long-term therapy (13).

Health care structures

In the public sector, the limited resources in terms of hospitals, equipment, drugs, and physicians and other health personnel are concentrated in the urban areas (14, 15). In the private sector, the lack of purchasing power of the rural population also keeps these health care services confined mainly to the urban areas.

The health care services have organizational problems and suffer from inadequate communication among the various levels, from the central ministerial authorities to providers at the most local levels.
The personnel partly or fully licensed to give patient care, including drug prescriptions, consists of health workers with widely varying degrees of training, from the minimally trained rural health worker to the specialist physician with advanced postgraduate training obtained abroad.

**Drug registration**

Some developing countries have no registration of drugs, while others have only established a national regulatory authority in the past ten years. In the majority of countries that have developed a control authority, the evaluation and approval process is unable to prevent the marketing of drugs with unproven or nonexistent efficacy, or with unacceptable toxicity. Various factors may contribute to the problem (16–23): the registration procedure may be in the hands of interested professional bodies rather than of the government health authority; the law may provide an inadequate basis for imposing adequate requirements; the necessary professional resources may be lacking; and objective information may be inadequate to form a judgement. In many countries that do have some form of evaluation, it is limited to pharmaceutical matters (such as quality) and takes no account of therapeutic value or appropriateness to national needs.

The deficiencies of regulation are especially evident in the flourishing private sector, where such regulatory mechanisms as may exist can cope neither with the influx of new products nor with the plethora of existing ones. Where a policy has emerged for the selection, procurement and use of essential drugs (9,24), its implementation in the public sector may prove more feasible although, in practice, purchasing based on drug tenders may complicate drug control and cause delay in the highly desirable harmonization between the private and the public sector.

**Public versus private drug sector**

In almost all developing countries, the private sector controls the major share of the drug market, according to various United Nations reports (Table 5). The lack of a sufficient and timely supply of drugs is nevertheless a critical issue in these countries, primarily because both the private and the public supply are skewed towards the urban areas, leaving the rural areas with little or no supply of drugs.

The public sector supply and distribution systems are generally deficient; they suffer from a shortage of funds and qualified personnel.
Table 5. The relative shares (in terms of US $) of pharmaceuticals distributed through the private and public sector services, as a percentage of the total pharmaceuticals consumed in 37 developing countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage share</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Private sector</td>
<td>Public sector</td>
</tr>
<tr>
<td>Argentina</td>
<td>93.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Pakistan</td>
<td>93.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Thailand</td>
<td>92.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>91.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Nepal</td>
<td>90.9</td>
<td>9.1</td>
</tr>
<tr>
<td>Paraguay</td>
<td>90.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Philippines</td>
<td>90.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>87.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Singapore</td>
<td>85.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Belize</td>
<td>83.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Brazil</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Chile</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>India</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Maldives</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Uruguay</td>
<td>80.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>78.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Mexico</td>
<td>77.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Barbados</td>
<td>76.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Peru</td>
<td>75.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Venezuela</td>
<td>74.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Grenada</td>
<td>72.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Saint Kitts and Nevis</td>
<td>71.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Colombia</td>
<td>70.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>70.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Saint Vincent and the Grenadines</td>
<td>64.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Jamaica</td>
<td>60.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Malaysia</td>
<td>60.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>57.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Antigua and Barbuda</td>
<td>53.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Myanmar</td>
<td>51.6</td>
<td>48.4</td>
</tr>
<tr>
<td>Bolivia</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Dominica</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Monserrat</td>
<td>47.0</td>
<td>53.0</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>45.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>43.0</td>
<td>57.0</td>
</tr>
<tr>
<td>Saint Lucia</td>
<td>42.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Guyana</td>
<td>35.0</td>
<td>65.0</td>
</tr>
</tbody>
</table>
and an unwieldy bureaucracy that delays procurement and distribution. Because of the deficiency of information, drug needs are not properly estimated and, where drugs are obtained, deficiencies in storage conditions and transport can cause them to be lost (9).

In the private sector, problems relate to the confusion caused by the availability of drugs of doubtful efficacy and safety, to prices that put products out of reach, to the existence of illegal channels of distribution, and to the unequal distribution of private pharmacies caused by the rural population's lack of purchasing power (14, 15, 25).

Drugs that might be considered to require a physician's prescription can generally be obtained over the counter, as any legislation that may exist on the distinction between prescription and nonprescription drugs is inadequately enforced.

Diagnostic resources
In developing countries, drugs tend to be used to make up for deficiencies in diagnostic resources. In many places, even simple diagnostic resources that are routinely used in the more advanced industrialized countries are not available. When available, their reliability may be questionable, leading to much irrationality in drug management.

In one study, more than 90% of antibiotic usage was empirical, on clinical grounds alone. The authors attributed this to limited facilities for microbiological testing and lack of confidence in the tests performed, since the results of sensitivity tests in two different laboratories often varied widely (26). The problem has been profiled in a recent report on antibiotic use and antibiotic resistance worldwide (27).

Drug Utilization Research in Developing Countries

Descriptive studies
A limited number of drug utilization studies has been conducted in developing countries. As was the case until recently in the industrialized countries (28–32), these studies have been mainly of a descriptive nature. Most have been drug-oriented, i.e. quantitative studies of drug utilization patterns in terms of prescriptions or sales. They have been limited in scope (medically, socially or economically), and the methods and units of measurement used have not been such as to allow comparative (intra- or intercountry) analyses.

The results of these few studies nevertheless help to profile some of the problems along the chain of drug utilization, relating variously to
distribution, prescribing and use. Such problems have, for more than a decade, been the focus of attention of national and international consumer bodies as well as of groups of health professionals (33–37).

**Studies of costs**
The earliest studies of drug utilization in developing countries examined drug costs (38–40). This work showed that most of these countries were spending around 40–60% of their public health budget on procuring pharmaceuticals, compared with 8–20% for the advanced industrialized countries. This comparison, although it alerted the finance ministries in developing countries, did not reveal the real reason for the great differences. The figures are comparative values and depend on other components of the public health budget, particularly health workers' salaries, which are very high in advanced industrialized countries compared with developing countries. The differences in the relative share of the drug budget in the total public health budget are therefore mainly due to the differences in the costs of services in the industrialized and developing countries. If one looks at the absolute figures rather than the percentages, however, one is struck by the very limited budget for public health care in many developing countries.

A rather more realistic analysis is that of the consumption of drugs per head. Table 6 gives the consumption of drugs per head as a percentage of the GNP per head in developed and developing countries. It shows that developed and developing countries allocate about the same share of their GNP to drugs but, because the GNP is so much

<table>
<thead>
<tr>
<th>Gross national product per head (US $)</th>
<th>Drug consumption per head (US $)</th>
<th>Drug consumption per head (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed countries</td>
<td>8105</td>
<td>62.5</td>
</tr>
<tr>
<td>Developing countries</td>
<td>626</td>
<td>5.0</td>
</tr>
</tbody>
</table>

lower in the latter, the absolute amount devoted to drugs is inadequate. It is unrealistic to expect developing countries to increase substantially their budget allocation for drugs, except in line with the progressive rise of their GNP. For a long period ahead, therefore, they will urgently require drug utilization studies to determine whether limited resources are being used to the best possible effect.

Studies of prescribing habits
Quantitative studies of prescribing have been more common. Although they employ various methods, they usually indicate (or at least suggest) certain irrationalities in prescribing. The therapeutic classes of drug that have been singled out have been the antibiotics and vitamin and tonic preparations.

Methodological approaches in descriptive studies
Table 7 presents some methodological approaches used in studying drug utilization in developing countries and the information obtained.

In certain countries, centralized purchase or inventory records (45–47), hospital inpatient records (48–57) or prescription forms (58–66) may be available and these have been used to conduct descriptive studies of drug utilization, though they are of variable quality. Unfortunately, in many developing countries, these records are not kept or are not available for research.

Unobtrusive observation has been used as a method to study drug consumption (75). Drug purchases in two cities of India were recorded in this way (69), in a representative sample of pharmacies, according to a selected schedule. Information was collected on the use of western drugs versus ayurvedic medicines, whether the purchase was physician prescribed or self-prescribed, and the type and amount of information available on the prescription form. This method has also been used to study pharmacists’ prescribing practices in Asian (71) and other countries.

Questionnaire methods have been employed to study physicians’ perceived sources of information and their stated practices compared with their actual behaviour (76). Similar methods have more recently been adopted to characterize the public’s perception of health, disease and drug interventions (77–81).

Hypothesis-generating systems in postmarketing surveillance
Few efforts have been made in developing countries to establish spontaneous reporting systems for monitoring adverse drug reactions.
Table 7. Methodological approaches used to study drug utilization in developing countries and the information obtained

<table>
<thead>
<tr>
<th>Methodological approach</th>
<th>Information obtained (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of commercial drug catalogue</td>
<td>Marketing of obsolete antibiotics (41)</td>
</tr>
<tr>
<td></td>
<td>Double standards in commercially provided drug information (42–44)</td>
</tr>
<tr>
<td>Review of centralized purchase/inventory data</td>
<td>Patterns of drug purchase/consumption (45–47)</td>
</tr>
<tr>
<td>Review of hospital inpatient records</td>
<td>Patterns and/or appropriateness of drug prescribing (48–57)</td>
</tr>
<tr>
<td>Review of prescription forms</td>
<td>Patterns and/or appropriateness of prescribing (58–66)</td>
</tr>
<tr>
<td>Questionnaires and review of records</td>
<td>Drug use before hospital admission (67)</td>
</tr>
<tr>
<td></td>
<td>Drug use in a rural community (68)</td>
</tr>
<tr>
<td>Direct observation of provider–consumer interaction</td>
<td>Drug prescribing by physicians (69,70)</td>
</tr>
<tr>
<td></td>
<td>Drug prescribing by pharmacists/pharmacy attendants (71)</td>
</tr>
<tr>
<td></td>
<td>Drug purchases and information provided at the pharmacy (71,72)</td>
</tr>
<tr>
<td></td>
<td>Drug sellers in a rural setting (73)</td>
</tr>
<tr>
<td>Unobtrusive observation and subsequent interview</td>
<td>Understanding and retention of medical advice (74)</td>
</tr>
</tbody>
</table>

Indonesia and Thailand participate in a WHO network; some other countries are still struggling with the organizational problems involved (82,83). Isolated attempts have been made to follow the same course in parts of Latin America. The problems encountered are similar to, although greater than, those already reported for the more developed countries: underrecognition of adverse drug reactions, lack of motivation to report, fear of litigation, work overload, and lack of trained personnel to conduct monitoring and perform the subsequent analysis (82–87).
Transferability of Drug Utilization Studies

The issue of the transferability of drug utilization research, in its current expanded form, has three aspects: basic research designs, data collection methods and results, all with pertinent evaluation and interpretation.

Basic research designs
The basic research designs used, whether they be descriptive, analytical, or experimental and epidemiological (medical or social), are applicable regardless of the setting and local conditions. As pointed out above, most or all studies in developing countries so far have been essentially descriptive, and training is needed in the more rigorous experimental and observational hypothesis-testing epidemiological approaches. Approaches from the social sciences are also sorely needed to identify and understand the factors involved in drug utilization, particularly at the consumer level.

Data collection methods
Some of the techniques, particularly those developed to assess drug safety, such as the monitoring of prescriptions, and the use of large computerized databases, may be difficult to implement in many developing countries, given the range of problems outlined above. Nevertheless, the basic principles of research design remain the same. Data may still be collected using simplified epidemiological sampling techniques, as the primary sources of information do not change. The great emphasis that has been placed on computerized data collection systems and medical linkage systems in industrialized countries is due to the greater availability there of certain resources, such as systems for processing pharmacy and medical billing claims, and affordable and trained personnel to collect data. In developing countries, the problem of acquiring sufficiently large databases may be solved by standardizing data collection, followed by collaboration between institutions and even countries.

Results
The relevance to developing countries of results obtained from studies in the industrialized countries depends on the local situation. At least some local data on utilization and the factors affecting it will be required from the developing country to determine whether the
situation is sufficiently similar to that elsewhere to justify cross-country extrapolation.

Ironically, the priority accorded to drug utilization research around the world is almost inversely proportional to the need for it. The examples of such research of the descriptive type that are available in the developing world are a promising start, but they do not contribute substantially to the process of therapeutic audit or to the creation and monitoring of a health and drug policy.

Essential drugs concept and policy
Drug utilization studies are not ends in themselves, but instruments in a comprehensive drugs (and health) policy (88). An increasing number of developing countries have adopted (at least on paper) an essential drugs concept and policy; this involves developing a rational approach to meeting the needs of a given population, by a scientific evaluation of drug efficacy and safety that is relevant to that population’s most pressing needs in the given economic and social situation (24). The elements of an essential drugs policy and the role of drug utilization studies may be seen in Table 8.

An essential drugs policy provides a framework for establishing priorities in drug utilization research in a developing country. What are the most pressing problems? What is the role of drugs in the solution to those problems? How effective is the implementation of the policy? What measures may be required to make necessary adjustments and how effective are they? Without an essential drugs policy, the impact of drug utilization studies will be minimal or nonexistent, as the information produced will effectively be lost and make no contribution to the quality of health care (89, 90).

Primary health care programmes
Primary health care programmes are being promoted and established to meet health care needs in developing countries. Interaction with such programmes provides opportunities for assessing the role of drugs and other interventions in the improvement of health. A primary health care programme is also the appropriate site for monitoring the need for and effectiveness of health care interventions. If health personnel, whether rural health workers or general practitioners, take an active role in drug utilization studies, this will help them develop a critical approach to the provision of health care in general, and to drugs in particular, and thereby improve the quality of care they give (91, 92).
Table 8. Major elements in the establishment of a national essential drugs (and health) policy

1. Qualitative and quantitative identification of real health needs; consideration of the scientific justification for the preventive and therapeutic use of drugs and vaccines, in relation to potential alternatives (compilation and validation of available demographic, health and drug statistics, initiation of complementary studies and analyses, pooling and digestion of relevant documentation)

2. Synthesis, setting of priorities and goals according to circumstances (morbidity/mortality pattern, economic and personnel resources, infrastructure, sociocultural and climatic factors, etc.)

3. Development of realistic plans for short-term and long-term implementation, including correction of existing skews (public versus private sector, among others), considering the organization and allocation of responsibilities, including needs for and possibilities of external assistance

4. Creation, adjustment and coordination of functional mechanisms for implementation, such as:
   - drug legislation and regulation (criteria and rules for drug evaluation, selection, quality control, prescribing, reimbursement, etc.);
   - drug logistics (supplies (make or buy?), inventory/stock, storage, distribution and delivery, dispensing, prescription and use);
   - programme promotion (adjustment of information, teaching and training for the relevant categories of personnel and the public, improvement of communication between the partners);
   - financing of the various enterprises

5. Establishment of a set of descriptive and analytical drug utilization surveys, integrated with a comprehensive and functional drug and health audit, for the purpose of evaluation and reevaluation of the various decisions and actions taken, for example in research and development

Source: Baksaas & Lunde (88).
Training programmes
Drug utilization studies can link the need for training with the actual content of training at both the undergraduate and the postgraduate levels, because they address the problems of the real world of clinical practice. At the undergraduate level, the concepts of drug utilization and essential drugs are rarely incorporated in the curricula for medicine, dentistry, pharmacy and nursing. By addressing the conditions and problems of routine health care delivery, appropriate studies of utilization will provide a rational basis for the strategy and contents of the undergraduate training of health workers at all levels.

Postgraduate continuing education programmes have generally not yet been established in developing countries. Drug utilization studies can serve not only as a tool to indicate the needs for information at this level, but also as a mechanism for developing and teaching a critical (scientific) approach to health care delivery through participation in relevant research. Several experiments in establishing networks of general practitioners interested in research suggest that this is feasible. Despite the limitations imposed by conditions in developing countries, drug utilization studies offer great opportunities to link drug selection, research and training (92,93).

International cooperation
Multicentre multidisciplinary approaches have been discussed in the more advanced industrialized countries as a means of overcoming logistic limitations in pharmacoepidemiological research. Multicentre national and/or international studies may be necessary if one is to collect appropriate study populations large enough to produce valid and generalizable results in the developing world. Given the constraints imposed by the limited financial and human resources, international collaboration (among developing countries themselves, and between these and the industrialized nations) seems to be an appropriate way of overcoming these limitations (94). The International Agranulocytosis and Aplastic Anemia Study is an example of such international multicentre and multidisciplinary collaboration (95,96). Initiatives to establish collaborative research networks in the developing countries as a group include the African Drug Utilization Research Group (97), the Medicines and Society group of Asian countries (98) and more recently the Central American Drug Utilization Research Group.
Conclusion

The need for drug utilization studies as a means of assessing the effectiveness and efficiency of drug use is greater in developing countries than elsewhere. The methods used in such studies, however, have been developed and tested mainly in the industrialized countries; although some drug utilization studies have been conducted in developing countries, they are few and mainly descriptive. Further studies using more rigorous epidemiological, sociocultural and economic approaches are urgently needed. They will have greater impact if conducted within the framework of the essential drugs concept and policy. Local conditions have to be taken into account when selecting and adapting methods developed in the industrialized countries, but rigorous and relevant research may be possible using simple, standardized data collection methods and involving primary care workers. Multidisciplinary (health and social sciences) approaches are necessary to decide whether and when to select relevant design strategies to improve the effectiveness and efficiency of drug utilization. International collaboration among developing countries and between these and the industrialized countries should be undertaken in the context of the transfer of relevant methodology and knowledge in drug utilization studies. That is above all a great challenge for clinical pharmacology.

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Medicines are part of our everyday lives. But how many drugs do people take and what sort, how much do they cost, and who influences the way they are prescribed and the way they are actually taken? The surprising answer is that we still do not know as much as we should. But drug utilization research is rapidly filling in the gaps.

This book describes the latest research methods and their use by the members of the WHO Drug Utilization Research Group. In the early days, the development of electronic data processing coincided with the growing need to monitor drug use. This enabled the comprehensive collection of data. Drugs were classified and defined so that valid comparisons became possible. Since then, studies have moved on to more sophisticated analyses: international comparisons show wide variations in the costs of drugs, in the relative share of different drugs in the market, in the proportion of the health budget spent on drugs and in the relation of the health budget to GNP.

As a more holistic concept of people’s health takes hold, a broader view is taken of the use of drugs. Studies of compliance (which assume the prescribing physician is the main influence on the patient) have widened to incorporate all the social and cultural influences that affect the patient as a consumer.

Every country needs a drug policy to make the most rational and cost-effective use of a very expensive part of the health service. Drug utilization research provides the tools for them to do so. This book is not just a record of achievements in that field; it is also a guide to students and researchers as well as people in the pharmaceutical industry.