Part IV

Selected Applications of Pharmacoepidemiology

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Studies of Drug Utilization

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Historical Background

Interest in drug utilization studies began on both sides of the Atlantic in the early 1960s. There was recognition of the virtual explosion in the marketing of new drugs, the wide variations in the patterns of drug prescribing and consumption, growing concern about delayed adverse effects, and increasing concern about drug expenditure, as reflected in the increase in both the monetary sales and the volume of drug prescriptions [1,2]. However, the development of pharmacoepidemiologic methods can be characterized by two different lines of work (drug utilization studies as performed in Europe versus pharmacoepidemiology as performed in the US), approaching each other from opposite directions, strongly influenced by variations in availability and accessibility of data sources.

Drug utilization studies at the national and international levels have been more developed in Europe, and pioneered by the Nordic countries, Scotland, the Czech Republic, and Northern Ireland. Under the auspices of the World Health Organization (WHO) Regional Office for Europe, a Drug Utilization Research Group was established in the 1970s to stimulate interest in studies comparing drug utilization between countries using a common methodology [1]. Factors that contributed greatly to this line of development, primarily in the countries of Northern Europe, have been the relatively small size of the populations involved, the limited number of pharmaceutical products on the market (2000–3000 in Norway and Sweden), and the availability of centralized statistics on wholesaler sales or dispensed prescriptions [1]. The early drug utilization studies were conducted during a time when data were not computerized and when there was no uniform classification system for medicines. However, with the growth of registers and computer technology, the size of the population is less of an issue and studies can be conducted on large populations. During the last decades, national databases with patient-level data on prescription medicines have been established in most European countries, but there is still a lack of comprehensive databases on medicines used in inpatient care [3,4].

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Drug utilization studies in Europe were originally predominantly quantitative, describing and comparing patterns of utilization of specific groups of drugs according to geographic regions and time. For example, international comparative studies have documented wide variations in the utilization of antidiabetic [1,5], psychotropic [6], nonsteroidal anti-inflammatory drugs (NSAIDs) [7,8], antihypertensive [1,6], antibiotic [9], and lipid-lowering drugs [10] in European and other countries. Longitudinal studies on the utilization of antidiabetic and antihypertensive drugs in some of these countries indicate that the differences cannot be explained only by differences in the prevalence of disease [11,12], and studies on, for instance, lipid-lowering agents have shown that the large increases in statin utilization were not associated with a subsequent decrease in coronary heart disease (CHD) mortality [13]. This illustrates that drug utilization patterns are complex and dependent on a range of factors. Furthermore, there is substantial room for improvement in the quality of medicines use; that is, how patients use medicines.

National studies have also revealed striking variations in drug utilization between regions and communities within the same country [1,6]. However, most of these studies have been descriptive and only a few of them have addressed the relation between variations in drug sales and treatment outcomes [14]. Since many of the studies have an ecologic design, examining associations between exposure and outcome in populations rather than individuals, they cannot directly be interpreted as associations at the level of the individual.

In Canada and the US, drug utilization research developed on a smaller scale, primarily at institutional or local health program levels. Factors that have hindered studies at a national level were originally the size of the population, the number of pharmaceutical products on the market (20 000–30 000), and the lack of an all-encompassing pharmaceutical data collection system [15]. Data on drug use are more readily available from health plans, health delivery institutions, and public healthcare programs. For example, early studies of physician prescribing showed that prescribing patterns varied greatly among physicians, according to their place and type of practice and the community in which they prescribed [16]. North American drug utilization research placed greater emphasis on studying the quality of physician prescribing practices, in particular with respect to antibiotics, in both hospital and outpatient settings [17–19]. This was followed by studies that targeted medications for cardiovascular diseases [20–23]. Studies describing national patterns of drug utilization and expenditures in the US are scarce [15], while those addressing the use of various types of medications, including herbal and other natural products, in adults and children are performed more often [24–27].

Drug utilization research has also developed in Latin America, Australia, Asia, and Africa. In Latin America, a drug utilization research group (the Latin American Group for Drug Utilization, DURG-LA) was founded in 1991 [28]. Over the years Latin American drug utilization researchers have conducted a wide range of studies on rational use of medicines, often using primary data collection in people's homes, in pharmacies, or in health facilities. Secondary data on drug utilization have traditionally been fragmented and difficult to access in Latin America [29]. There has been a rapid development of drug utilization research in low- and middle-income countries. In the early 1990s, the WHO and the International Network for the Rational Use of Drugs (INRUD) published a simple sampling method and a standard set of indicators to describe core aspects of prescribing and dispensing [30]. The first International Conference on Improving the Use of Medicines (ICIUM), held in Chiang Mai, Thailand, in 1997, systematically reviewed interventions to promote rational drug use in developing countries [30]. Substantial problems of irrational use of

medicines were identified and some key areas were highlighted for future research, such as interventions to improve the use of antibiotics and antimalarial drugs, methods to assess the impact of Drugs and Therapeutic Committees, and the impact of financial incentives on drug utilization patterns. During the last decade, we have witnessed a rapid growth of large prescription databases in Asia [31]. It is likely that these will further contribute to the globalization of drug utilization research.

Definitions

Drug utilization research can be defined as "an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines and for the testing of interventions to enhance the quality of these processes" [32]. This definition includes both quantitative and qualitative research methods.

The WHO defined drug utilization as the "marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences" [33]. Some authors have suggested that the development of drugs relative to health priorities should also be included in studies of drug utilization [34]. This broad definition differs from the narrower one that appeared in the North American literature, "the prescribing, dispensing and ingesting of drugs" [35,36].

In the US, drug utilization review (DUR), or drug use evaluation (DUE), refers to an authorized, structured, ongoing review of prescribing, dispensing, and use of medication (see Chapter 19). It involves a comprehensive review of patients' prescription and medication data before, during, and/or after dispensing to ensure appropriate medication decision making and positive patient outcomes. As such, DUR is a quality assurance measure [37].

In all of these definitions, recognition is granted, explicitly or implicitly, of the nonclinical (e.g., socio-anthropological, behavioral, and economic) factors influencing drug utilization. Studies of the process of drug utilization focus on the factors influencing and events involved in the prescribing, dispensing, administration, and taking of medication. However, the broader definitions of the WHO, the Academy of Managed Care Pharmacy (AMCP), and the European Drug Utilization Group go beyond the "process" of drug utilization, which is the movement of drugs along the therapeutic drug chain, to include consideration of the various outcomes, such as use of drugs of doubtful or no clinical efficacy, and the quality of drug use [38]; that is, the degree to which it adheres to established norms. According to these definitions, studies of drug utilization include not only studies of the medical and nonmedical factors influencing drug utilization, but also the effects of drug utilization at all levels, from the individual patient to the society. Studies of how drug utilization relates to the effects of drug use, beneficial or adverse, are usually labeled analytic pharmacoepidemiologic research. These two aspects of the study of drug utilization have developed along parallel lines, but may now be regarded as interrelated and part of a continuum of interests and methods.

As stated by Lunde and Baksaas [39], the general objectives of drug utilization studies are:

> problem identification and problem analysis in relation to importance, causes, and consequences; establishment of a weighted basis for decisions on problem solution; assessment of the effects of the action taken. These objectives are relevant to problems and decision making throughout the drug and health chain. The approaches may vary according to the purpose and the needs of the users. Those include the health authorities, the drug manufacturers, the academic and

clinical health professionals, social scientists, and economists as well as the media and the consumers.

Since many drug utilization studies have a strong focus on health policy, the discipline may be seen as the bridge between pharmacoepidemiology and health services research. It is also closely connected to clinical pharmacology, with the principal aim of drug utilization research being to facilitate the safe and effective use of medicines in populations [40].

This chapter focuses on the current status of descriptive epidemiologic approaches to the study of the processes of drug utilization and analytic studies on factors associated with drug utilization patterns. The epidemiologic approaches to the study of the beneficial and harmful effects of drug utilization are covered elsewhere in this book.

Clinical Problems to Be Addressed by Pharmacoepidemiologic Research

In order for a drug to be marketed, it must be shown that it can effectively modify the natural course of disease or alleviate symptoms when used appropriately, for the right patient, with the right disease, in the proper dosage and intervals, and for the appropriate length of time. Used inappropriately, however, drugs often fail to live up to their potential, with consequent morbidity and mortality and waste of resources.

Drug utilization research describes the extent and pattern, quality, determinants, and outcomes of drug exposure. Pattern of use covers the extent, profiles, and trends in drug use and costs over time. It gives answers and helps understand how drugs are used in terms of incidence, prevalence, and trends over time. Quality of use is determined using audits to compare actual use to national prescription guidelines or local drug formularies. Indicators of quality of drug use may include the choice of drug (adherence with the guideline or formulary), drug cost (compliance with budgetary recommendations), drug dosage (awareness of interindividual variations in dose requirements and age dependence), awareness of drug interactions and adverse drug reactions, and the proportion of patients who are aware of or unaware of the costs and benefits of the treatment.

Drug utilization research may generate hypotheses for further investigation by comparing drug utilization patterns and costs between different regions or time periods and by comparing observed patterns of drug use with current recommendations and guidelines for the treatment of a certain disease. These considerations should include both underuse and overuse of drugs. Determinants of use include user characteristics (e.g., sociodemographic parameters and attitudes towards drugs), prescriber characteristics (e.g., specialty, education, and factors influencing therapeutic decisions), and drug characteristics (e.g., therapeutic properties and cost).

A number of studies have addressed the factors that influence prescribing decision making, including education, advertising, colleagues, working circumstances, personality, control and regulatory measures, demands from society and patients, and cultural factors [41–43]. Some controversy exists concerning the relative impact of the various sources of influence on prescribing behavior, particularly the influence of pharmaceutical advertising. In studies of hospital practice the following factors have been stated to contribute to inappropriate prescribing: simple errors of omission; physician ignorance of cost issues in prescribing; failure to review medication orders frequently and critically; inability to keep up to date with developments in pharmacology and therapeutics; insulation of physicians and patients from cost considerations because of third-party coverage; and lack of communication between physicians and pharmacists [44].

Cultural factors are known to play a role in illness behavior and drug prescribing/consumption. A popular model describing cultural differences that may also influence drug prescribing is Hofstede's model of cultural dimensions. Five cultural dimensions are defined by which countries may be scored: power distance, individualism, masculinity, uncertainty avoidance, and long-term orientation. Power distance refers to the degree of hierarchy in a country and the extent to which the less powerful members of organizations and institutions accept and expect that power is distributed unequally. Individualism refers to the prevalence of the interests of an individual versus the group and the degree to which individuals are integrated into groups. Masculinity refers to a culture in which the emotional roles of the two genders are clearly separated. The assertive, competitive pole has been called "masculine" and the modest, caring pole "feminine." Uncertainty avoidance deals with a societal tolerance for uncertainty and ambiguity. It indicates to what extent a culture programs its members to feel either uncomfortable or comfortable in unstructured situations. Long-term orientation values are thrift and perseverance, while short-term orientation values are respect for tradition, fulfilling social obligations, protecting one's "face" [45]. It has been found that power distance and uncertainty avoidance are cultural dimensions associated with higher antibiotic use, suggesting that hierarchical societies use more antibiotics (difficulties dealing with authority), whereas more egalitarian societies use fewer, and in societies that tend to avoid uncertainty antibiotics have a defensive function (as the prescriber and the patient aim for certainty) [46,47].

Drug utilization research enables assessment of whether interventions to improve drug use had the desired impact, as well as the extent to which other factors influenced the pattern of use, including regulatory changes, reimbursement policy, pharmaceutical industry promotional activities, and others.

Intervention strategies aimed at improving prescribing behavior in hospital as well as primary care settings have been critically reviewed [48–51]. These are discussed in Chapter 19 and include dissemination of printed educational materials alone; multimedia warning campaigns; drug utilization audit followed by mailed or interactive feedback of aggregated results; group education through lectures or rounds; use of computerized reminder systems; use of opinion leaders to informally endorse or support specific behavior change interventions; one-to-one education initiated by a drug utilization expert; required consultation or justification prior to the use of specific drugs; and use of clinical guidelines.

Drug utilization research addresses the medical, social, and economic aspects of drug use [32,52]. Even when used appropriately, drugs have the potential to cause harm. However, a large proportion of their adverse effects is predictable and preventable [53,54]. Adverse drug reactions and drug nonadherence are important causes of hospital admissions in both adult and pediatric patients [54–56] (see also Chapter 38). Studies in the US have estimated that adverse drug events account for up to 28% of emergency department visits and 25% of ambulatory care encounters; up to 70% of these visits are deemed preventable [57]. Similar figures are also found in the UK and Sweden [54,58,59].

Many of these drug-related admissions may be preventable through the application of existing principles and data [60,61]. The situations that may lead to preventable adverse drug reactions and drug-induced illness include the use of a drug for the wrong indication; the use of a potentially toxic drug when one with less risk of toxicity would be just as effective; the concurrent administration of an excessive number of drugs, thereby increasing the possibility of drug–drug interactions (see Chapter 40); the use of excessive doses, especially for pediatric or geriatric patients; and continued use of a drug after evidence becomes

available concerning important toxic effects. Many contributory causes have been proposed: excessive prescribing by the physician; failure to define therapeutic endpoints for drug use; the increased availability of potent prescription and nonprescription drugs; increased public exposure to drugs used or produced industrially that enter the environment; the availability of illicit preparations; and prescribers' lack of knowledge of the pharmacology and pharmacokinetics of prescribed drugs [53]. Increased morbidity or mortality due to medication error [62] (see Chapter 41), poor patient adherence [63] (see Chapter 38), discontinuation of therapy [64–66], and problems in communication resulting from modern-day fragmentation of patient care are also to be considered (see Chapter 39).

Medication underdosing and underprescribing are often overlooked and can result in poor patient outcomes. The failure of physicians to prescribe an effective drug or effective doses for a treatable disease is a significant concern. For example, in a geographic area of Sweden with a higher suicide rate than average for the country, sales of antidepressant drugs were about half of those in other areas [67]. In the US, the underuse of beta-blockers in elderly patients with myocardial infarction was associated with an increased risk of death [20]. Other studies have documented significant underuse of antithrombotic drugs [21,68,69], lipid-lowering therapy [66,70–72], beta-blockers [22], aspirin [73], and thrombolytics [23] in patients with appropriate indications, but where outcomes were not assessed. In addition, underuse of beneficial medications may have other reasons, such as lack of access due to economic reasons or geographic access to the pharmacy and availability of prescription drugs [74–76].

Therapeutic practice, as recommended by relevant professional bodies, academic researchers, and opinion leaders, is initially based predominantly on data from premarketing clinical trials. However, the comparative effectiveness (i.e., the effectiveness of one medication compared to another medication in the real-world setting; see Chapter 26) and safety of new agents cannot be known with certainty until a drug has been on the market for many years or been extensively used. Complementary data from clinical experience and studies in the postmarketing period may result in changes in indication (e.g., a specific antibiotic no longer being a choice due to antimicrobial resistance), treatment duration (e.g., short-course antibiotic treatment of community-acquired pneumonia in children under 5 years of age), regimen (e.g., changes due to tolerance to oral hypoglycemic agents), precautions and contraindications (e.g., gastrointestinal bleeding with NSAIDs), and safety-based withdrawals [77,78]. For instance, when serious adverse reactions or special problems occur, particularly those that may lead to death or serious injury, a prominently displayed boxed warning, the so-called black box, is added to the US Food and Drug Administration (FDA) labeling of drugs or drug products. As therapy recommendations are updated through guidelines and other approaches, drug utilization studies must address the relationship between therapeutic practice as recommended and actual clinical practice [79].

Methodologic Problems to Be Solved by Pharmacoepidemiologic Research

There are several methodologic issues in drug utilization research. Most of them are the same as for other pharmacoepidemiologic studies and are well described in other parts of the book. In this section, some specific issues of importance related to the different study designs in drug utilization are described, along with an overview of the available data sources.

Study Designs

There are many types of drug utilization studies. Research methods in drug utilization can be either *quantitative* or *qualitative*. Quantitative research deals with quantities; data are presented in numeric figures in categories or rank order and measured in various units. Quantitative research usually starts with a predefined hypothesis or theory, followed by data collection to provide an answer to the research questions formulated. Associations between variables and differences between different categories may be studied by using different statistical methods. Qualitative research, on the other hand, refers to the examination, analysis, and interpretation of observations for the purpose of discovering underlying meanings and patterns of relationships [80]. Qualitative studies include information that is not in numeric form collected through focus group discussions, open-ended questionnaires, in-depth interviews, and observations. Such studies may be used to explore the views of prescribers, dispensers, and patients in dealing with medicines. Consequently, they are important to gain a deeper understanding of various phenomena in drug utilization. Qualitative drug utilization studies are not further described in this chapter. For further reading on qualitative studies, there is a separate chapter on qualitative methods in drug utilization research in the handbook on drug utilization research [81].

The simplest quantitative drug utilization studies are descriptive. Such studies identify patterns or trends in drug utilization, without any attempt to draw conclusions about factors influencing drug use. Objectives of descriptive studies may be to quantify the present state, developmental trends, and time course of drug usage at various levels of the healthcare system, whether national, regional, local, or institutional. Routinely compiled drug statistics or drug utilization data that are the result of such studies can be used to estimate drug utilization in populations by age, sex, social class, morbidity, and other characteristics, and to identify areas of possible over- or underutilization. They also can be used as denominator data for calculating rates of *reported* adverse drug reactions in the context of spontaneous reporting systems (see Chapter 10); to monitor the utilization of specific therapeutic categories where particular problems can be anticipated (e.g., narcotic analgesics, hypnotics and sedatives, and other psychotropic drugs); or as markers for very crude estimates of disease prevalence (e.g., antiparkinsonian drugs for Parkinson's disease); to plan for drug importation, production, and distribution; and to estimate drug expenditures [34].

Descriptive drug utilization studies may also address quality of drug prescribing, dispensing, or use. In these studies, explicit predetermined criteria are created against which aspects of the quality, medical necessity, and appropriateness of drug prescribing may be compared. Drug use criteria may be based on such parameters as indications for use, daily dose, or length of therapy. Other possible criteria for poor drug prescribing include the failure to select a more effective or less hazardous drug if available, the use of a fixed combination drug when only one of its components is justified, or the use of a costly drug when a less costly equivalent drug is available [82]. In North America, these studies are known as *drug utilization review* (DUR) studies. For example, a large number of studies in North America have documented the extent of inappropriate prescribing of drugs, in particular antibiotics, and the associated adverse clinical, ecologic, and economic consequences [17–19].

Analytic drug utilization studies aim to gain a deeper understanding of the explanatory factors behind utilization patterns. The most robust analytic study designs are cohort studies or case–control studies. In traditional pharmacoepidemiology, such studies are used to assess the effectiveness or safety of drug therapy, where drug utilization is the exposure and clinical events constitute the outcome. In analytic drug utilization studies, drug exposure is the outcome

and the explanatory factors behind drug use constitute the exposure. The same methods for matching or confounder adjustment could thus be applied as for cohort and case–control studies used to assess safety or effectiveness. These methods are well described in other chapters of this book (see Chapter 43). Some examples of cohort studies in drug utilization include persistence studies, where discontinuation is the outcome to drug treatment [83–85]. Theoretically, case–control studies may also be conducted, selecting subjects on the basis of whether they have (or had) been prescribed or dispensed the drug of interest or not. An investigation of previous exposure to a factor might reveal whether there is an association between the drug utilization and previous exposure. Such studies are scarce in the literature, however.

In the absence of individual-level data to link drug utilization to other factors, ecologic studies could be conducted. In these studies, group-level data on dispensed or prescribed drugs are compared with other datasets, either for different geographic areas or population groups at a certain point in time or for the same population at different times. Some examples of ecologic studies in drug utilization research include the associations between antidepressant use and suicide [86]; respiratory medication prescribing, air pollution, and deprivation [87]; coronary heart mortality and statin use [88]; and unemployment rates and prescription drug utilization patterns [89]. Ecologic studies are simple to conduct, but they have limited value since no individual linkage has been conducted between exposure and outcome. Consequently, the correlations found in these studies cannot be interpreted as associations at the individual patient level.

Types of Data on Drug Utilization

A considerable amount of drug use data may be obtainable or is already available, the usefulness of which depends on the question at hand. All the data have certain limitations in their direct clinical relevance [90]. For quantitative studies, the ideal is a count of the number of patients in a defined population who ingest a drug of interest during a particular time frame, with a certain diagnosis or indication. The data available are only approximations of this for reasons that are described shortly, and thereby raise many questions about their presentation and interpretation.

Since most statistics on drug consumption were compiled for administrative or commercial reasons, the data were usually aggregated and expressed in terms of volumes or expenditure. First, data on drug utilization can be available as total costs or unit cost, such as cost per package, tablet, dose, or treatment course. Although such data may be useful for measuring and comparing the economic impact of drug use, these units do not provide information on drug exposure in the population. Moreover, data on expenditure are influenced by price fluctuations over time, distribution channels, inflation, exchange rate fluctuations, price control measures, and so on [91].

Volume data may be available from manufacturers, importers, or distributors as the overall weight of the drug that is sold or the unit volume sold; that is, the number of tablets, capsules, or doses sold. However, tablet sizes vary, making it difficult to translate weight into even the number of tablets. Prescription quantities also vary, so it is difficult to translate number of tablets into the number of exposed patients.

The number of prescriptions (either written or dispensed) has traditionally been one of the most frequently used measures in drug utilization studies. This measure may have some relevance in studies of medicines given for short treatment courses, such as antibiotics. For medicines used for chronic treatment the value is limited, since different patients receive a different number of prescriptions in any given time interval, and the amount allowed to prescribe or dispense on a prescription may vary substantially between countries. To translate

the number of prescriptions into the number of patients, one must divide by the average number of prescriptions per patient, or else distinctions must be made between first prescriptions and refill prescriptions. The former is better for studies of new drug therapy, but will omit individuals who are receiving chronic drug therapy. Additional problems may be posed by differences in the number of distinct drugs written in each prescription. Finally, it should be noted that these aggregate measures of prescribed or dispensed volumes represent approximate estimates of true consumption. The latter is ultimately modified further by the patients' actual drug intake; that is, their degree of adherence.

In the context of DUR, drug utilization data may be presented in the form of prescribing profiles for individual physicians or practices according to the number, monetary value, and even type of prescription ordered during a given time period. Pharmacies may also be ranked according to the number, cost, and type of prescription dispensed for similar intervals. However, these gross measures of prescription activity and drug use are limited in their capacity to reflect the wide spectrum of specific problems in prescribing. For example, they ignore problems such as the wrong drug for the indication, the wrong drug for the patient, the wrong dose, the wrong dosing interval, and the wrong duration of therapy. Also, one's deviation from the practices of the mean practitioner is not a good measure of one's "appropriateness" as a provider. Purely quantitative data characterizing prescribers as "high" or "low" may be driven, for example, by the number of patients seen by the physician and the type and severity of the patients' diseases. Data presented by pharmacy are even less informative, since patients may be dispensed prescriptions from an unknown range of different healthcare providers. However, for studies of medicine use in hospitals and studies of over-the-counter (OTC) products, pharmacy sales data may provide important information. Finally, it is important to emphasize that data on expenditures are not necessarily indicative of appropriateness, whether high or low relative to the mean.

In recent years, large patient-level prescription databases have become increasingly available [3]. They may contain all dispensed prescription drugs regardless of the reimbursement status and irrespective of who the prescriber is. These data are also closer to estimating actual drug exposure compared to prescribing data from electronic health records. However, there may be problems of poor sensitivity, with patients having other ways of receiving medications (e.g., drugs purchased abroad, OTC medicines, or drugs "borrowed" from relatives), or poor specificity, with patients not taking the drugs they have purchased. There are many useful methods available for studying drug utilization using individual data on dispensed prescriptions. Based on experiences from Denmark, Hallas and Støvring discussed three nonspecific analytic templates that could be applied to individual-level data on dispensed prescriptions [92]. Such methods include the ratio of prevalence odds to incidence rate to estimate the average duration for drug use, the Lorenz curve, and the waiting time distribution. The Lorenz curve expresses skewness in drug use. It shows the proportion of drug use that is accounted for by percentiles of drug users, ranked according to their volume of drug intake. It may express the extent of heavy users as well as sporadic small-volume users and may, for example, be used to screen for an unsuspected abuse potential of a drug. Figure 18.1 illustrates the use of insulin in a defined population: 50% of the users used 76% of the volume [92].

The waiting time distribution is a frequency distribution of first occurrences of drug use within a time window (Figure 18.2). It forms the basis for estimates of prevalence and incidence rate. Furthermore, it displays visual correlates of epidemiologic prescribing parameters such as

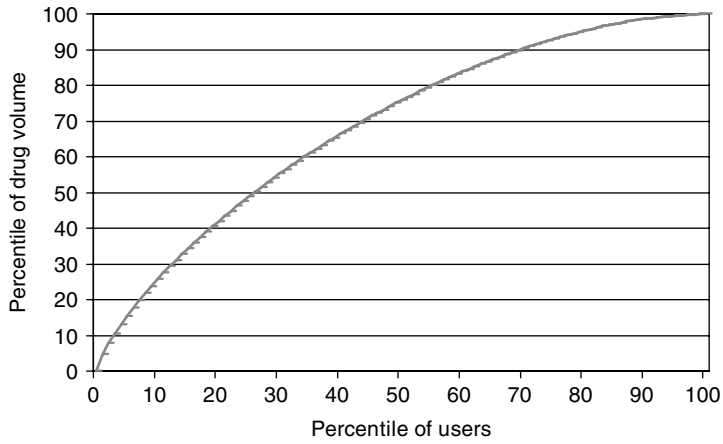


Figure 18.1 Lorenz curve for insulin use. The graph shows the proportion of insulin use that is accounted for by percentiles of insulin users, ranked according to their annual insulin consumption. Data from county of Funen, Denmark, 2003. *Source:* Hallas J, Støvring H. Templates for analysis of individual-level prescription data. *Basic Clin Pharmacol Toxicol* 2006; **98**(3): 260–5, Figure 1. Reproduced with permission of John Wiley & Sons.

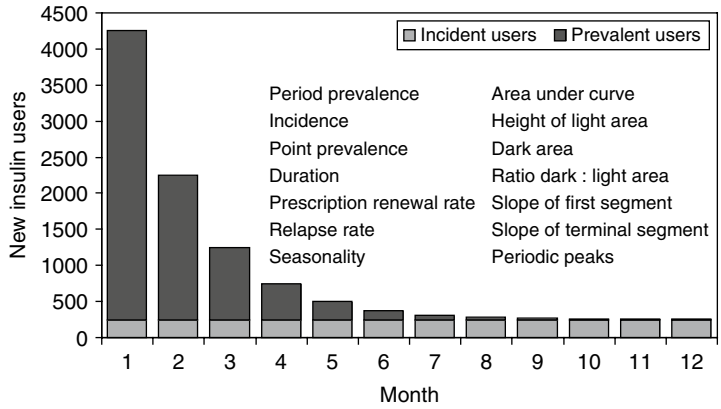


Figure 18.2 Visual correlates of various measures of insulin use. Hypothetical curve. Data from county of Funen, Denmark 2003. *Source:* Hallas J, Støvring H. Templates for analysis of individual-level prescription data. *Basic Clin Pharmacol Toxicol* 2006; **98**(3): 260–5, Figure 3. Reproduced with permission of John Wiley & Sons.

period prevalence, point prevalence, incidence rate, duration, prescription renewal rate, relapse of treatment, and seasonality.

From a quality-of-care perspective, to interpret drug utilization data appropriately, there is a need to relate the data to the reasons for the drug usage. Data on morbidity and mortality may be obtained from national registries (general or specialized); national samples where medical service reimbursement schemes operate; *ad hoc* surveys and special studies; hospital records; physician records; and patient or household surveys. "Appropriateness" of use must be assessed relative to indication for treatment, patient characteristics (age-related physiologic status, sex, habits), drug dosage (over- or underdosage), concomitant diseases (which might contraindicate or interfere with the chosen therapy), and the use of other drugs (interactions). However, no single source is generally available for obtaining all of this information. Moreover, because of incompleteness, the medical record may not be a very useful source of drug use data [93,94].

Generally agreed standards or criteria for appropriateness, based on currently available knowledge, are essential elements of the DUR process. These criteria must be based on scientifically established evidence; updated regularly according to new scientific evidence; explicitly

stated (to ensure consistency in evaluations); and applicable to a given setting. The development and standardization of these criteria are major undertakings. Finally, for DUR programs, even the strategy to be used to optimize one's intervention is still unclear.

Data Sources

A large variety of data sources can be used for drug utilization research. They may provide either primary or secondary data [95]. Primary data sources refer to original data collected by the investigator conducting the research for a specific purpose [96]. Secondary data sources include already collected data; that is, data which have not been usually generated for a specific research purpose but can be adapted to the analysis of a new research question [95].

Drug utilization studies have been conducted using a large variety of secondary data sources, including sales registries, procurement records, reimbursement/claims databases, medical records, pharmacy dispensing records, pharmacy stock records, disease-based registries, and population health surveys. The availability of such data varies substantially between countries, but there has been a large growth in access to them over time everywhere. The ongoing digitalization of healthcare brings further opportunities to access large amounts of clinical data for DUR. Some of these data may be unstructured and tricky to analyze, but new techniques and methods have been developed to address these challenges.

In the earlier editions of this book, we listed some diagnosis-linked and non-diagnosis-linked computer databases for drug utilization studies, as well as providing an overview of historical databases important for the development of pharmacoepidemiology and drug utilization research. In this edition, electronic databases are discussed in separate chapters (Chapters 11–14) and here we briefly give an overview of some types of sources that may be used. A more comprehensive overview of secondary data sources may be found in a recent textbook on drug utilization research [97].

Drug utilization data may be collected at any point in the pharmaceutical supply chain, starting with the manufacturer, passing through wholesalers and pharmacies, and ending with patients. Aggregate level sales data (from manufacturer/wholesaler/pharmacy) or purchases (from purchaser/payer, e.g., hospitals or community pharmacies) are regularly collected in most countries. Such data do not contain any information on number of patients, or any clinical data. Consequently, these data have limited value in analytic studies on the effectiveness and safety of medicine use. Still, they may be valuable in studies assessing quality of medicine use or to assess the effect on interventions in health systems. They may also be used in ecological studies comparing utilization patterns with other data, generating hypotheses to be studied with more robust study designs. At pharmacies, drug dispensing data may be recorded at an individual patient level. These data may subsequently be collected by insurers or reimbursement agencies. Such patient-level databases provide valuable sources for drug utilization, with and without linkage to other clinical information. Finally, healthcare providers are another important source of data on drug utilization studies, with information on drugs prescribed to patients available in their health records. Healthcare providers may also report information on selected drugs to disease-based patient registries.

Aggregated sales data have been used in drug utilization research for decades. Today, most countries keep some records of drug sales, at a regional or national level. These data can be obtained from health authorities [4,5] as well as from private companies such as IQVIA, a well-known commercial source of drug utilization data. An overview of European databases performed by Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) indicates

that aggregate sales data are widely collected across Europe [3,4]. In the US, the IQVIA National Sales Perspective database documents sales data for prescription drugs, OTC products, and some self-administered diagnostic products. Data collected include volume of dollars and quantities moving from manufacturers in various outlets within all states. In Canada, the IQVIA CompuScript database contains data on prescriptions sold from about two-thirds of Canadian retail pharmacies. Sales data collected by authorities or by companies such as IQVIA may be the only secondary source available to studies conducted in regions where other databases are not yet established or not accessible.

Dispensing data containing unique identifiers of patients are regularly collected at pharmacies. Since patients visit a pharmacy to fill their prescriptions, such data provide a more appropriate estimation on actual drug exposure than prescribing data from electronic health records. However, it is important to acknowledge that patients may also have other ways of obtaining medications (e.g., purchasing abroad, receiving in inpatient care, or "borrowing" from relatives), Furthermore, even though the patient claimed the prescription, it is uncertain whether the patient has taken the medicine as indicated by the prescriber. In Europe, the first patient-level research databases were established in the late 1960s to early 1970s [76]. These databases were based on prescriptions dispensed at the pharmacies and primarily used to study drug utilization. They were too small for drug safety studies. In the 1980s and 1990s larger databases were created, also based on administrative data, such as prescriptions dispensed at pharmacies, in Scotland [40], Denmark [98], Italy [99], and the Netherlands. An example of such a dispensing database is the Swedish Prescribed Drug Register, established in 2005, containing data with unique patient identifiers for the entire population of 10 million inhabitants for all dispensed prescriptions in ambulatory care [100]. This registry includes data on the patient (age, sex, personal identification number, place of residence), dispensed drug (Anatomic Therapeutic Chemical [ATC] classification code, defined daily dose [defined shortly] number, prescribed dose, package, reimbursement, date of prescribing and dispensing), prescriber (profession, specialty, workplace), and pharmacy (identifier, location). It can be linked to many other registers including outcome data and many quality registers with clinical data for different diseases. A recent review summarized the scientific output from the register after the first decade [101].

In many countries, third-party payers (public or private) collect medication data from pharmacies for billing purposes. Drug reimbursement/claims databases typically contain unique patient identifier, prescriber (either individual prescriber and/or clinic/practice), pharmacy dispensing the drug, drug name and ATC code, strength, dosage form, quantity dispensed, date of prescription and dispensation, days' supply, as well as patient co-payment and total drug expenditure. In some countries reimbursement data also include information on diagnosis, as an International Classification of Diseases (ICD) code is written on prescriptions. Reimbursement databases are commonly used in DUR. A limitation, though, is that they may only contain those drugs that are reimbursed. Furthermore, they are sensitive to changes in co-payment over time. There are also differences between health systems in regulations and reimbursement and, consequently, the amount of information documented in these databases varies. In some countries, prescription drugs are funded only for selected groups of the population (e.g., the elderly) [102,103], and various other public and private prescription plans may be used for other population groups.

In countries with many different insurers (e.g., in the US), it may be difficult to follow people over time, since patients move in and out as their insurance eligibility changes [104]. In the

US, Medicaid medical and pharmaceutical billing data have been available for drug utilization studies for many years. With the disadvantaged and disabled population included in Medicaid, however, the generalizability of the results is a potential concern, especially for such descriptive studies. In contrast, in many European and some Asian countries with national health systems, insurance coverage can be close to 100% of the population, thus providing a complete picture of medicine use in these countries [4,105].

Large databases are also derived from electronic health records. The key advantage of these databases is that they contain clinical data such as diagnoses. One example is the General Practice Research Database® (GPRD®) in the UK (see Chapter 14), which is based on medical records from general practitioners (GPs). Hundreds of GPs contribute anonymized patient information to a central database, that now contains millions of patients. Included are prescriptions issued by the GP but with no information from the pharmacy (compliance/adherence). All these databases were primarily used for drug safety studies, but have also been used to study drug utilization [96,106].

Another example is the Integrated Primary Care Information (IPCI) database, established at Erasmus University in the Netherlands. It consists of the computer-based patient records of 150 general practitioners. To date the database has accumulated data on approximately 500 000 patients. The records are coded to ensure the anonymity of patients; data include patient demographics, symptoms (in free text), diagnoses (based on the International Classification for Primary Care and free text), clinical examination findings, referrals, laboratory test results, hospitalizations, and physician-linked drug prescriptions and dosage regimen (but no information from the pharmacy on compliance/adherence).

The National Disease and Therapeutic Index (NDTI), by IQVIA, is an ongoing study of physician prescribing that is conducted mainly for use by pharmaceutical companies for marketing [107]. This study employs a rotating sample of office-based physicians, who record all patient encounters and corresponding "drug mentions" for two-day periods four times a year. A special prescription form is used to collect information on the drug (specific product, dosage form, new vs. continuing therapy), patient characteristics (sex), prescriber (specialty, location, region), type of consultation (first versus subsequent), concomitant drugs and diagnoses, and the desired pharmacologic action [15]. Data have been made available to academic researchers (for a fee) and the FDA [15]. Although useful for studies of prescribing, longitudinal patient-specific studies are not possible with this database.

Currently Available Solutions

DUR studies are activities aimed at the detection and quantification of problems. They should be distinguished from DUR *programs*. DUR studies are usually one-time projects, not routinely conducted. They provide only minimal feedback to the involved prescribers and, most importantly, do not include any follow-up measures to ascertain whether any changes in drug therapy have occurred. A DUR program, on the other hand, is an intervention in the form of an authorized, structured, and *ongoing system* for improving the quality of drug use within a given healthcare institution. The quality of drug prescribing is evaluated by employing predetermined standards for initiating administrative or educational interventions to modify patterns of drug use that are not consistent with these standards. The measurement of the effectiveness of these interventions is ideally an integral part of the program [108,109].

In the US, DUR programs (commonly known in hospitals as DUE programs) are part of the quality assurance activities required by

Medicaid–Medicare regulations, the Joint Commission, the former Professional Standards Review Organizations (PSRO), and Section 4401 of the Omnibus Budget Reconciliation Act of 1990 [109]. In Europe, DUR programs have been proposed as periodic "therapeutic audits" performed at various levels (patient, prescriber, hospital, county, municipality, country, and groups of countries), assessing not only the clinical consequences of drug utilization, but also the social and economic consequences. These studies are to be followed by whatever feedback is felt to be necessary and appropriate to effect changes in therapeutic practices [6,110,111]. Most commonly, these therapeutic audits have been based on aggregate data analysis of medicines consumption at a national level and interventions, usually regulatory or informational and educational, and are aimed accordingly at whole populations or subgroups, rather than specific individuals. Despite their widespread implementation in the US, the effectiveness of DUR programs in reducing prescribing errors and improving patient outcomes remains to be established (as discussed later).

Units of Measurement

The defined daily dose (DDD) method was developed in response to the need to convert and standardize readily available volume data from sales statistics or pharmacy inventory data (quantity of packages, tablets, or other dosage forms) into medically meaningful units, to make crude estimates of the number of persons exposed to a particular medicine or class of medicines [112].

The DDD method is useful for working with readily available gross drug statistics; allows comparisons between drugs in the same therapeutic class and between different healthcare settings or geographic areas, and evaluations of trends over time; and is relatively easy and inexpensive to use. The method is firmly established in Europe and is increasingly used by researchers in other regions [113–118]. A WHO manual on drug utilization research provides an overview of the method [119]. Guidelines for classifying medicines and their assigned DDDs are updated annually by the WHO Collaborating Centre for Drug Statistics Methodology (www.whocc.no).

The DDD is a technical statistical unit defined as the assumed average daily maintenance dose for a drug for its main indication in adults. It is only a measurement unit and does not necessarily reflect the prescribed or recommended dose. To enable comparison of drug use in DDDs the information has to be presented with an adequate denominator; that is, the population that was exposed to a drug. Ambulatory drug use is commonly expressed as DDDs per 1000 inhabitants per day. For chronically used drugs, it can be interpreted as the proportion of the population that receives treatment with a particular medicine on any given day. For example, if the use of a drug is measured as 30 DDDs/1000 inhabitants/day in a given country, this indicates that around 3% of the country's population receives that drug daily. Sometimes better estimates can be given by adjusting the denominator for a target population (e.g., for oral contraceptives the denominator is females below 45 years of age). For use in hospital settings, the unit is expressed as DDDs per 100 bed-days (adjusted for occupancy rate); it suggests the proportion or percentage of inpatients that receive a DDD in a day. For example, 30 DDDs/100 bed-days indicates that 30% of patients in a day receive a certain drug. For medicines that are used in the outpatient setting for short-term periods, such as antimicrobials, the unit is expressed as DDDs per inhabitant per year; this provides an estimate of the number of days for which each person is treated with a particular medication in a year. For example 8 DDDs/inhabitant/year indicates that every inhabitant is on average treated with that drug for 8 days in a year.

The DDD method has been useful in describing and comparing patterns of drug utilization [1,2,111], providing denominator data to estimate reported adverse drug reaction rates [120], performing epidemiologic screening for problems in drug utilization [111], and monitoring the effects of informational and regulatory activities [113,121]. It has also been used to study variations in antimicrobial utilization [9,122,123], as well as antimicrobial utilization and its correlation with antimicrobial resistance in outpatient [123,124] and inpatient settings in Europe [125], and to report on sustained reduction of antibiotic use and low bacterial resistance with implementation of a multidisciplinary, coordinated national antimicrobial and rational use program [126].

The European Surveillance of Antimicrobial Consumption Network, ESAC-Net (formerly ESAC), collects and analyzes data on antimicrobial consumption from European Union (EU) and European Economic Area/European Free Trade Association (EEA/EFTA) countries, using the DDD methodology. The data on community and hospital antimicrobial consumption are publicly available from ESAC-Net [127].

The DDD method should be used and interpreted with caution. The DDD is not a recommended or a prescribed dose, but a technical unit of comparison; it is usually the result of literature review and available information on use in various countries. Thus, the DDDs may be high or low relative to actual prescribed doses. Moreover, the DDDs refer to use in adults. Since children's doses are substantially lower than the established DDDs, if unadjusted this situation will lead to an underestimation of population exposures, which may be significant in countries with a large pediatric population. Although pediatric DDDs have also been proposed [128], the concept and its applicability have not been incorporated into the WHO method [119]. Finally, DDDs do not take into account variations in adherence.

The prescribed daily dose (PDD) is another unit, developed as a means to validate the DDD. The PDD is the average daily dose prescribed, as obtained from a representative sample of prescriptions [129]. Problems may arise in calculating the PDD because of a lack of clear and exact dosage indication in the prescription, as is often the case with the prescribing of insulin. Prescriptions for chronic therapy, as in the case of insulin, may be refilled many times and the dosage may be altered verbally between prescribing events [130]. For certain groups of drugs, such as oral antidiabetics, the mean PDD may be lower than the corresponding DDD. Up to twofold variations in the mean PDD have been documented in international comparisons [129]. Higher PDDs have been observed in the US relative to Sweden for commonly prescribed drugs, such as hydrochlorothiazide, diazepam, and oxazepam [131]. In studies assessing whether antidepressants increase the risk of suicide, a refined person-year of use estimate was obtained from adjusting the DDD by the average PDD for individual antidepressants [132]. Although the DDD and the PDD may be used to estimate population drug exposure "therapeutic intensity," the method is not useful to estimate incidence and prevalence of drug use, or to quantify or identify patients who receive doses lower or higher than those considered effective and safe.

The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) have recommended days of therapy (DOT) for expressing antimicrobial drug use [133]. DOT is the number of days when at least one dose of a medication was administered irrespective of dose or route of administration. They are not impacted by dose adjustments and can be used in both adult and pediatric populations. Similar to PDDs, expressing drug use in the number of DOTs requires patient-level use data, which may not be feasible at every facility.

Drug and Disease Classification Systems

The Anatomic Therapeutic Chemical classification system is generally used in conjunction with the DDD method [112,119]. It was originally

developed by the Norwegian Medicinal Depot, which became a WHO Collaborating Centre for Drug Statistics Methodology; the center is now located at the Norwegian Institute of Public Health (www.whocc.no). The ATC system is based on the main principles of the Anatomical Classification system developed by the European Pharmaceutical Market Research Association (EPhMRA) and the International Pharmaceutical Market Research Group (IPMRG).

The ATC system consists of five hierarchical levels: a main anatomical group, two therapeutic subgroups, a chemical-therapeutic subgroup, and a chemical substance subgroup. The coding of furosemide preparations is used to illustrate the ATC classification structure in Table 18.1. The first three levels are modifications of the three-level EPhMRA and IPMRG classification system. The fourth and fifth levels are extensions that are developed and updated by the WHO Collaborating Centre for Drug Statistics Methodology. Ongoing discussions aim to identify differences in the two classification systems and harmonize the first three levels. Statistics reported with the ATC system should not be directly compared with figures prepared with the EPhMRA system.

Medicinal products are classified according to the main therapeutic indication for the principal active ingredient. Most products are assigned only one ATC code. However, some active medicinal substances may have more than one ATC code, if the drug has different uses at different strengths (acetylsalicylic acid as a platelet aggregation inhibitor and as an analgesic–antipyretic), dosage forms (timolol to treat hypertension and to treat glaucoma), or both (medroxyprogesterone for cancer therapy and as a sex hormone). Prednisolone is an example of a drug that has six different codes. Fixed-dose combination products pose classification difficulties. For example, a combination product that contains an analgesic and a tranquilizer is classified as an analgesic, even though it also contains a psychotropic substance. Because the ATC codes and DDDs may change over time with regular revisions, researchers must carefully document which version of the classification and DDD assignment is used, so that the resulting drug statistics may be adequately interpreted [134].

The European Drug Utilization Research Group (EuroDURG), formerly the WHO Drug Utilization Research Group and currently an association of European national Drug Utilization Research Groups, and the International Society of Pharmacoepidemiology Special Interest Group in Drug Utilization Research (ISPE SIG DUR) recommend the use of the ATC classification system for reporting drug consumption statistics and conducting comparative drug utilization research [130]. The WHO International Drug Monitoring Program uses the system for drug coding in adverse drug reaction monitoring (www.who-umc.org). Some developing countries also use the ATC system to classify their essential drugs [135,136]; this may eventually lead to the preparation of annual drug utilization statistics [137].

In the US, the Iowa Drug Information System (IDIS) is a hierarchical drug coding system that is based on the three therapeutic categories of the American Hospital Formulary Society (AHFS), to which a fourth level was added to code individual drug ingredients [138]. The IDIS code has eight numeric digits, two digits per level (see Table 18.1). This coding system was used in the Established Populations for Epidemiologic Studies of the Elderly survey [138]. Other coding systems such as the National Drug Code and the Veterans' Administration Classification [139] do not provide unique codes for drug ingredients.

In the UK, British National Formulary (BNF) codes are widely used for drug utilization studies. The BNF provides monographs for drugs available in the UK. The numbering system is produced by NHS Prescription Services, part of the NHS Business Services Authority in England [140].

Table 18.1 Anatomic Therapeutic Chemical (ATC) and Iowa Drug Information System (IDIS) classification and coding structures for furosemide.

ATC Classification (C03CA01)					
C	Cardiovascular System (First level, main anatomical group)				
	03	Diuretics (Second level, main therapeutic group)			
		C	High-ceiling diuretics (Third level, therapeutic subgroup)		
			A	Sulfonamides, plain (Fourth level, chemical therapeutic subgroup)	
				01	Furosemide (Fifth level, chemical substance)
IDIS Classification (40280401)					
40	Electrolyte Solutions (First level, main therapeutic group)				
	28	Diuretics (Second level, therapeutic subcategory)			
		04	Loop-diuretics (Third level, therapeutic subcategory)		
			01	Furosemide (Fourth level, chemical substance)	

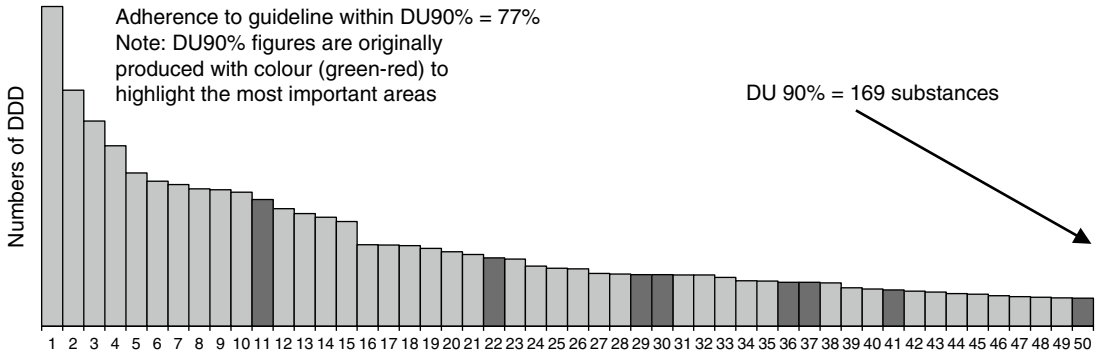
The International Classification of Diseases is a system of diagnostic codes for classifying diseases and other health problems. The ICD is published by the WHO and used worldwide in morbidity and mortality statistics, drug reimbursement systems, and automated decision support in healthcare. The system includes categories relating to medicinal substances, but in the context of adverse outcomes, and often in quite broad terms. It does not include codes suitable for recording and classifying drug utilization [141].

The Systematized Nomenclature of Medicine (SNOMED) provides a core general terminology for use in various medical fields. SNOMED clinical terms (CT) contain more than 311 000 active concepts in clinical settings, organized in different hierarchies. An individual number represents each concept, and several concepts can be used in combination to describe a complex condition. Clinical finding/disorder and procedure/intervention are examples of the main levels in SNOMED CT. Substance and pharmaceutical/biologic product are also in the main levels. The pharmaceutical/biologic product hierarchy was introduced as a top-level hierarchy in order to distinguish drug products from their chemical constituents (substances). It contains multiple levels of granularity, used to support a variety of purposes, including electronic prescribing and formulary management (www.ihtsdo.org).

Quality Indicators

Drug utilization studies assessing the quality of drug prescribing involve the use of various types of quality indicators [142]. These may be defined as "A measurable element of prescribing performance for which there is evidence or consensus that it can be used to assess quality, and hence in changing the quality of care provided." Quality indicators for drug utilization may be classified based on the amount of clinical information incorporated in the indicator. *Drug-oriented indicators* focus solely on the drugs prescribed, dispensed, or consumed. The simplest approaches only require aggregate data on the volume and expenditure of prescribed or dispensed drugs. Such data could be presented as time trends or top-ten lists and used as a catalyst to stimulate discussion around areas for improvement in drug therapy. Simple drug-oriented indicators can be constructed to compare practices, clinics, or regions. Such drug-oriented indicators are based on drug data alone and can be used irrespective of the indication for which the drug is prescribed. The most commonly used drug-oriented indicator is the ratio between different drugs. Some examples include the ratio of COX-2 inhibitors to all NSAIDs measured in DDDs, the ratio of simvastatin to statins, and the ratio of angiotensin-converting enzyme (ACE) inhibitors to all renin-angiotensin drugs [143–146]. Other types of drug-oriented indicators have been focused on inappropriate drugs in children and the elderly [147–150].

Another approach analyzed the number of drugs that accounted for 90% of drug utilization (DU90%) and the percentage of these drugs that were included in evidence-based guidelines [151]. The first studies on the DU90% method used the guidelines on rational drug use issued by the regional Drug & Therapeutics Committee in Stockholm, Sweden [152]. (See Figures 18.3 and 18.4.) These guidelines consist of approximately 200 medicines recommended as first-line choices for the treatment of common diseases. The 90% level was arbitrarily selected to focus on the bulk of prescribing, yet allow some degree of individual variation. The number of different products in the DU90% segment varied between 117 and 194 among 38 primary healthcare centers in Stockholm; adherence to the guideline varied at between 56% and 74%. The Swedish Medical Quality Council has recommended the DU90% method for assessing quality in drug prescribing. Using this method, researchers in the Netherlands did not find any



	SUBSTANCE	(DDD)	DDD	% TOT	Rx	COST	COST/DDD
1	**Acetylsalicylic acid**	1 tablet	39,894,782	4.9%	650,808	22,995,814	0.58
2	**Simvastatin**	30 mg	29,455,125	3.6%	438,802	26,731,380	0.91
3	**Enalapril**	10 mg	25,632,413	3.2%	296,329	18,111,103	0.71
4	**Furosemide**	40 mg	22,513,352	2.8%	409,630	18,091,910	0.80
5	**Omeprazol**	20 mg	19,140,338	2.4%	399,298	30,122,076	1.57
6	**Cyanocobalamin**	1 mg	18,125,259	2.2%	319,737	11,711,704	0.65
7	**Amlodipine**	5 mg	17,685,421	2.2%	165,634	10,209,168	0.58
8	**Metoprolol**	0.15 g	17,160,653	2.1%	498,845	72,421,602	4.22
9	**Levothyroxine sodium**	0.15 mg	17,030,980	2.1%	405,353	23,094,330	1.36
10	**Ramipril**	2.5 mg	16,743,688	2.1%	95,412	8,323,952	0.50
11	Felodipine	5 mg	15,807,331	2.0%	177,725	13,901,701	0.88
12	**Candesartan**	8 mg	14,695,169	1.8%	118,979	59,427,671	4.04
13	**Zopiclone**	7.5 mg	14,059,603	1.7%	426,875	16,073,585	1.14
14	**Paracetamol**	3 g	13,597,335	1.7%	621,717	35,916,832	2.64
15	**Citalopram**	20 mg	13,065,325	1.6%	266,993	12,672,896	0.97
16	**Sertraline**	50 mg	10,178,236	1.3%	119,262	11,241,414	1.10
17	**Hydroc.thiazide + amiloride**	*	10,145,923	1.3%	120,927	5,066,822	0.50
18	**Calcium combinations**		10,047,562	1.2%	206,568	24,983,957	2.49
19	**Propiomazine**	25 mg	9,729,948	1.2%	174,248	12,173,527	1.25
20	**Metformin**	2 g	9,297,143	1.2%	152,190	18,415,868	1.98
...							
169							
DU 90%	**1 - 169**		727,456,526	90.0%	14,034,056	2,648,199,198	3.64
170 - 853			80,552,999	10.0%	2,699,117	2,370,147,348	29.42
TOTAL	**1 - 853**		**808,009,524**	**100.0%**	**16,733,173**	**5,018,346,546**	**6.21**

Bold = in guideline
**** = Different DDDs for various routes of administration***
Medicines without DDD excluded (455, corresponding to 511 million SEK)

Figure 18.3 DU90% (number of substances accounting for 90% of the volume in DDDs) in Stockholm Healthcare Region in 2009. Dark gray, nonrecommended drugs; DDD, defined daily dose; DU, drug utilization. *Source:* Gustafsson LL, Wettermark B, Godman B, *et al*. The "Wise List": a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. *Basic Clin Pharmacol Toxicol* 2011; **108**(4): 224–33, Figure 4. Reproduced with permission of John Wiley & Sons.

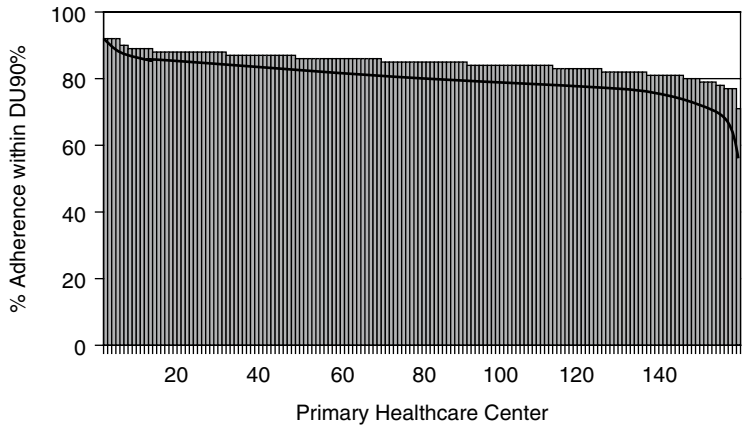


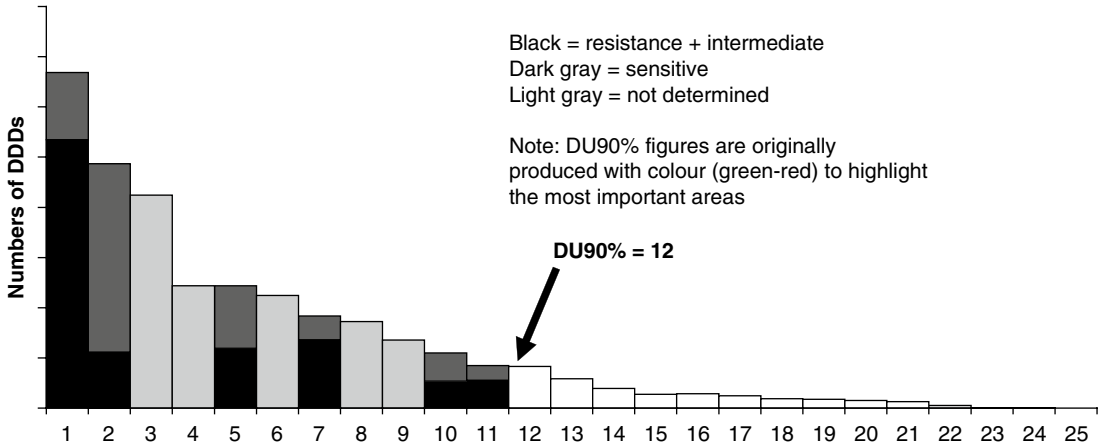
Figure 18.4 Adherence to "Wise List" recommendations for 156 primary healthcare centers for prescriptions dispensed in 2009. The thick black line equals the adherence range for the same practices in 2003. Observe that the order of the practices may differ between the two years. *Source:* Gustafsson LL, Wettermark B, Godman B, *et al*. The "Wise List": a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. *Basic Clin Pharmacol Toxicol* 2011; **108**(4): 224–33, Figure 5. Reproduced with permission of John Wiley & Sons.

association between different levels of performance in pharmacotherapy audit meetings and quality of prescribing for seven drug classes. They suggested that for certain drug classes, such as antidepressants, duration of treatment may be more relevant for quality prescribing than using the drug of first choice in the guidelines; for diabetes, co-medication with statins may be more important than the number of different oral antidiabetics; and for obstructive airway diseases, concomitant use of corticosteroids may be more a more appropriate criterion than choices within the guidelines [153].

DU90% has also been used, for example, to compare NSAIDs prescribing in Denmark, Italy, Croatia, and Sweden [7,8], antibiotics in Denmark and Italy 199], and general intensive care unit antibiotic prescribing and cost patterns in Israel [154], and to assess the effect of financial incentives linked to self-assessment of prescribing patterns in Swedish primary care [155]. In Stockholm, the DU90% profile was useful in following up adherence to recommendations of essential drugs in ambulatory care for 15 years [152,156]. Furthermore, integrating resistance to the antibiotic DU90% profiles showed striking figures on the use of antibiotics that were cheap but resistant rather than effective and more expensive [157]. (See Figure 18.5.)

Access to patient-level data enables the construction of more clinically relevant drug-oriented indicators linking different drugs to each other or over time. Some examples of approaches include the identification of inappropriate or interacting drugs (questionable combinations) prescribed to individual patients [60,61,150,158,159] or co-prescribing of beta-adrenoreceptor antagonists and agonists [160]. They may also be used to identify in which order drugs are initiated to patients, for instance the proportion of patients initiated on angiotensin receptor blockers previously dispensed ACE-inhibitors [161].

Disease-oriented indicators include information on drugs linked to the diagnosis or healthcare problem. They may either indicate to what extent patients are being treated with the recommended drugs for a certain condition, or to what extent drugs are avoided for patients with conditions for which the drugs should not be used.



	SUBSTANCE	(DDD)	DDD	% TOT	DDD/100 BED-DAYS	COST/DDD (rubles)	% RESIST
1	Gentamicin	0.24 g	6 687	20%	3,1	5	80%
2	Cefazolin	3 g	4 865	15%	2,3	41	23%
3	Amoxicillin + clav. acid	1 g	4 242	13%	2,0	105	nd
4	Ampicillin + Oxacillin	8UD (2g)	2 438	7%	1,1	13	nd
5	Benzylpenicillin	3.6 g	2 435	7%	1,1	129	49%
6	Pefloxacin	0.8 g	2 245	7%	1,1	6	nd
7	Ampicillin	2 g	1 838	6%	0,9	10	74%
8	Metronidazole	1.5 g	1 726	5%	0,8	50	nd
9	Lincomycin	1.8 g	1 357	4%	0,6	5	nd
10	Amikacin	1 g	1 099	3%	0,5	143	49%
11	Ciprofloxacin	1 g	845	3%	0,4	400	66%
12	Pipemidic acid	0.8 g	828	2%	0,4	22	nd
DU 90%	**1 - 12**		30 603	92%	14,4		
13 - 25			2 477	8%	1,2		
TOTAL	**1 - 25**		**33 080**	**100%**	**15,5**		

Figure 18.5 DU90% profile for "antibacterial for systemic use" (J01, ATC/DDD classification) in university hospital N2 of St Petersburg, Russia in 2003. The 12 antibiotics are ranked in order of number of defined daily doses (DDDs) corresponding to 90% of use (data from the hospital pharmacy). The black parts correspond to the percentage of resistance (resistance + intermediate) for the antibiotics, and the dark gray to the percentage of sensitivity. Antibiotics not tested for bacterial sensitivity are light gray. nd, not determined. *Source:* Goryachkina K, Babak S, Burbello A, Wettermark B, Bergman U. Quality use of medicines: a new method of combining antibiotic consumption and sensitivity data – application in a Russian hospital. *Pharmacoepidemiol Drug Saf* 2008; **17**(6): 636–44.

Patient-oriented indicators include information on drugs linked to individual clinical characteristics of the patient, such as the severity of the disease and whether a certain treatment is suitable for a specific patient [160].

Although the use of health insurance databases has been reported in countries outside North America, Europe, and Asia [31,162–164], medical and pharmaceutical databases are generally not available in most low and middle income countries. An approach based on the use of standardized criteria (indicators) to measure changes in medicines prescribing, dispensing, and patient care was developed in the

Table 18.2 World Health Organization/International Network for the Rational Use of Drugs drug use indicators.

Core indicators
Prescribing indicators
Average number of drugs per encounter
Percentage of drugs prescribed by generic name
Percentage of encounters with an antibiotic prescribed
Percentage of encounters with an injection prescribed
Percentage of drugs prescribed from essential drugs list or formulary
Patient care indicators
Average consultation time
Average dispensing time
Percentage of drugs actually dispensed
Percentage of drugs adequately labelled
Patient's knowledge of correct dosage
Facility indicators
Availability of copy of essential drugs list or formulary
Availability of key drugs
Complementary indicators
Percentage of patients treated without drugs
Average drug cost per encounter
Percentage of drug costs spent on antibiotics
Percentage of drug costs spent on injections
Prescription in accordance with treatment guidelines
Percentage of patients satisfied with care they received
Percentage of health facilities with access to impartial drug information

Source: How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators. EDM Research Series No. 007. Reproduced with permission of WHO.

early 1990s by INRUD and the WHO [165]. The approach has facilitated the study of drug utilization in developing countries. It includes recommendations on minimum sample sizes, sampling methods, and data collection techniques, depending on study objectives. The method recommends 12 core indicators and 7 complementary indicators to study drug use in health facilities (Table 18.2). These indicators can be used to describe prescribing practice [166], for conduct monitoring and supervision [167], and to assess the impact of interventions [168–170]. The WHO has compiled indicator results and other findings reported in studies conducted in 97 developing and transitional countries between 1990 and 2006 [171].

INRUD has also developed simple low-cost indicators to measure adherence to antiretroviral (ARV) treatment in resource-poor settings. Adherence measures derived from dispensing data in pharmacy records, self-report data in medical records, and attendance logs predicted key clinical outcome related to individual patient treatment success, and were feasible to collect [172]. The four indicators were percentage of patients with self-reported full adherence, percentage of days covered by ARVs dispensed, percentage of records with a 30-day gap in ARVs dispensed, and percentage of patients who attended within 3 days of the scheduled appointment. These indicators allow assessment and comparison of programs and facilities, and monitoring and evaluation of interventions.

Intervention Strategies Based on Drug Utilization Data

Numerous studies have described interventions aimed at improving prescribing by the use of drug utilization data obtained from drug utilization studies, and are discussed further in Chapter 19. Two intervention strategies may illustrate different approaches to the use of drug utilization data available from computer databases of office practice.

In a randomized clinical trial, Avorn and Soumerai [173] used Medicaid data to identify physicians who were prescribing drugs that were assessed as inappropriate (based on considerations of documented efficacy, relative efficacy, and relative cost). These physicians were targeted for educational or information activities, as either face-to-face contacts or written drug information. Schaffner *et al.* [174] and Ray *et al.* [175] used a similar approach in another controlled intervention study, comparing different strategies aimed at modifying physician prescribing behavior: written drug information versus personal visits by pharmacists versus personal visits by physician educators. These two studies demonstrated the efficacy of face-to-face methods in improving drug prescribing.

The second approach uses claims data to perform computerized screening for patients who may be at increased risk for drug-induced illness, using patient-specific medical and drug histories [176–178]. Health professionals then evaluate profiles of patients with possibly inappropriate drug use. If drug use is indeed considered inappropriate, a letter is sent to the prescriber providing a profile of the patient's relevant computerized claims record and a warning of the potential for drug-induced disease. Often the problem is a concomitant drug or diagnosis of which the prescriber was unaware. This approach is obviously much less expensive than the face-to-face approach. Using before-and-after comparisons, a significant reduction in drug-induced hospitalizations has been noted [177]. However, the interpretation of these results is hampered by the use of a nonexperimental design. Other authors have found no effect on measures of prescribing or on patient outcomes [179]. A simultaneously controlled trial is needed to adequately assess the value of this approach.

Many other studies have described intervention strategies based on providing drug utilization data feedback, alone or in combination with printed material and/or other "educational strategies," for example group discussions, lectures, seminars, or personal visits by "experts." The results from these studies are conflicting. Some suggest that methods that involve only feedback of drug utilization data or audit results are ineffective. Others suggest a transient effectiveness for those that combine the use of drug utilization review data with group discussions, lectures, and visits by experts. However, these are difficult to interpret because of limitations in their research designs [180].

Conceptually, DUR programs are aimed at the improvement of medical care and cost containment. However, in practice traditional approaches have focused on control of the abuse or overuse of drugs, polypharmacy, or patients obtaining prescriptions from many different prescribers. Moreover, most DUR studies have emphasized process measures of quality of care, for example the use of clinical laboratory tests to monitor for adverse effects during chloramphenicol or aminoglycoside therapy. The approach described by Strom *et al.* [176], Lee Morse *et al.* [177], and Groves [178] was a significant advance in DUR programs, as it was primarily aimed at improving measurable patient outcomes. Also, it does not impose arbitrary restrictions on drug use, potentially impairing patient care, but seeks to reduce costs by improving patient care. In seeking to reduce the financial impact of drug use, it does not focus on the drug costs themselves, but on the effects of the drugs. By reducing the need for medical care through the beneficial effects of drugs, or by increasing the need for remedial medical care because of drug toxicity, pharmaceuticals can have a financial impact on the healthcare system that is much larger than the cost of the drugs themselves. (This is discussed more in Chapter 35.)

Despite their appeal, the effectiveness of DUR programs remains to be established. A study of six Medicaid programs failed to identify an effect of retrospective DUR on the rate of potential prescribing errors and rate of all-cause or specific-cause hospitalizations [179]. Another study did not find effects of two state prospective DUR interventions on the frequency of drug problems, utilization of prescription drugs and other health services, and clinical outcomes [181].

The Future

Opportunities

Drug utilization research is rapidly expanding in all countries across the globe, from the early descriptive studies to advanced studies combining different data sources to further understand medicine use in the population. In the early days, drug utilization studies were suggested to focus on the medical, social, and economic

aspects of drug utilization [2]. Medical aspects included potential inappropriate prescribing in different groups such as children and the elderly. Social aspects included attitudes to medicines and health, drug abuse and dependence, and their causes and trends, as well as socioeconomic inequities. Economic aspects included drug prices and expenditure for generics and brands, as well as allocation of resources (money, personnel, facilities) to drugs and other aspects of healthcare. All these aims are still relevant for future drug utilization research. However, the types of drugs in focus will differ, with 42% of the substances in drug development being biologics, compared to 8% on the market today [182]. The growing pressures on all healthcare systems with aging populations, rising patient expectations, stricter clinical targets, and expensive new medicines will further increase the need for drug utilization studies to monitor that resources are used wisely and that new medicines are prescribed to those who may benefit most from them.

From a public health perspective, the observed differences in national and international patterns of drug utilization require much further study. The medical consequences as well as the explanations for such differences are still not well documented. The increasing availability of patient-level databases on dispensed medicines will facilitate studies of the incidence and prevalence of medicine use, as well as more sophisticated studies on patterns of use, including drug combinations, dosing regimens, and persistence to drug therapy. These databases contain or may be linked to diagnoses and other clinical data that facilitate drug utilization studies, where drug utilization can be understood in its clinical context. The ongoing digitalization of healthcare will further increase access to large amounts of data for drug utilization research. Considerable amounts of healthcare data are generated every day, some of it from data sources to a large extent unexplored or unused in drug utilization research, such as clinical records systems, mail traffic, social media, and various devices.

Numerous studies have addressed the factors influencing drug prescribing. However, the relative importance of the many determinants of appropriate prescribing is still to be adequately elucidated. Further research is needed to better define to what degree and which determinants of inappropriate prescribing are susceptible to modification, and what might be an appropriate mix of interventions to achieve optimal impact. Although regulation is effective, it is not possible to regulate all aspects of the clinical decision-making process to ensure optimal drug prescribing [183]. Other approaches in addition to educational and informational measures are being explored. It is also important to emphasize the growing role of the patient in drug utilization research, both as a source of information to understand how drugs are used in reality, and also as a partner in designing and conducting research.

There is a need too for many more intervention studies targeted at the various stakeholders involved in the process of prescribing, dispensing, and consumption of medicines. Many strategies aimed at modifying prescribing behavior have been proposed and adopted. The evidence to date indicates that mailed educational materials alone are not sufficient to modify prescribing behavior [173,180]. Early studies conducted in Australia [184] and Denmark [185] concluded that mailed, unsolicited, centralized, government-sponsored feedback, one based on aggregate prescribing data and the other with a clinical guideline, had no impact on physician prescribing. For interventions that have been shown to be effective in improving drug prescribing (discussed in Chapter 38), there is a need to further define their relative efficacy and proper role in a comprehensive strategy for optimizing drug utilization. Questions yet to be addressed through a proper methodology deal with the role of printed drug information such as drug bulletins; the duration

of effect of educational interventions such as group discussions, lectures, and seminars, each in both the outpatient as well as the inpatient settings; and the generalizability of face-to-face methods, as described by Avorn and Soumerai [173], Schaffner *et al.* [174], and Ray *et al.* [175]. There is also a need for more research on whether the benefits and savings achieved with intervention strategies outweighed the costs of performing the intervention.

More clinically applicable approaches to DUR programs, such as the computerized screening of patient-specific drug histories in outpatient care to prevent drug-induced hospitalizations, still require further development and assessment. Although numerous studies have described the results of these and other novel programs [177,178,186,187], adequate documentation of their efficacy in improving quality of care is an important subject for future work. Patient outcome measures as well as process measures of quality of drug utilization have to be included in such studies. To be effective and efficient, healthcare policy options should be based on sound scientific evidence [188].

Challenges

The use of computerized databases has greatly facilitated studies of drug utilization. Although useful, most of these databases are far from ideal, as they have been set up mainly for administrative purposes, such as reimbursement, and drug utilization data are obtained as "spin-off" information. The model information system that will suit both medical and administrative needs [189] is still unavailable, although there is increasing use of electronic medical records for routine practice in countries such as the Netherlands, Australia, the UK, and the US. There is also a general lack of patient-level databases on medicine use in inpatient care [190]. Existing medical and pharmaceutical databases, with all their described limitations, will continue to be the main resources for these drug utilization studies. There is, however, a rapid growth of data coming from other sources. Even though new computer techniques and machine learning have been developed, many challenges remain, such as how to deal with missing data, unstructured data, poor data validity, and interoperability.

We have been fortunate to live in an era when large amounts of drug utilization data have become available for research. It is important to recognize, however, that the increasing amounts of digitalized personal data may add fuel to the debate on confidentiality. Confidentiality of patient data has so far been successfully handled and procedures have been implemented in most countries that are consistent with the guidelines for good practice in data privacy, medical record confidentiality, and research developed by the International Society for Pharmacoepidemiology (ISPE). Still, it is important to acknowledge the ongoing debate. In the EU, a new data protection framework is being implemented in all member states. Similar initiatives are being taken in other countries. Hopefully, this will not prevent opportunities for conducting research.

Even though drug utilization analyses today are conducted routinely in most health systems, this does not imply that drug utilization research is awarded high priority. The recruitment and training of researchers may be hampered by limitations in funding, as well as limitations in career opportunities. These two problems impose constraints on the future development of studies in drug utilization. However, despite this, the search continues for simple and relatively inexpensive methods to conduct descriptive studies of drug utilization, and effective intervention strategies that may contribute to the optimization of drug therapy. Fortunately, the increasing commitment to drug utilization research is reflected in the development and growth of international groups such as ISPE (www.pharmacoepi.org) [191], the International Clinical Epidemiology Network (INCLEN; www.inclentrust.org) [192], EuroDURG (www.

eurodurg.com) [193], DURG-LA [28], and INRUD (www.msh.org/INRUD) [194,195].

In summary, the study of drug utilization continues to evolve. The development of computerized databases is allowing the linkage of drug utilization data to clinical data and much other information to get a better understanding of drug utilization. The WHO/INRUD indicator-based approach to drug utilization studies is facilitating the development of drug utilization research in developing and transitional countries. Many strategies have already been proposed, tested, and implemented to improve the quality of drug prescribing in developed [196] and developing countries [197]. DUR programs, particularly approaches that take into primary consideration patient outcome measures, merit further rigorous study and improvement. Opportunities for the study of drug utilization are still underexplored, but the political issue regarding the confidentiality of medical records, as well as limitations in funding and personnel, may limit the growth of drug utilization research.

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