Handbook of Clinical Pharmacology
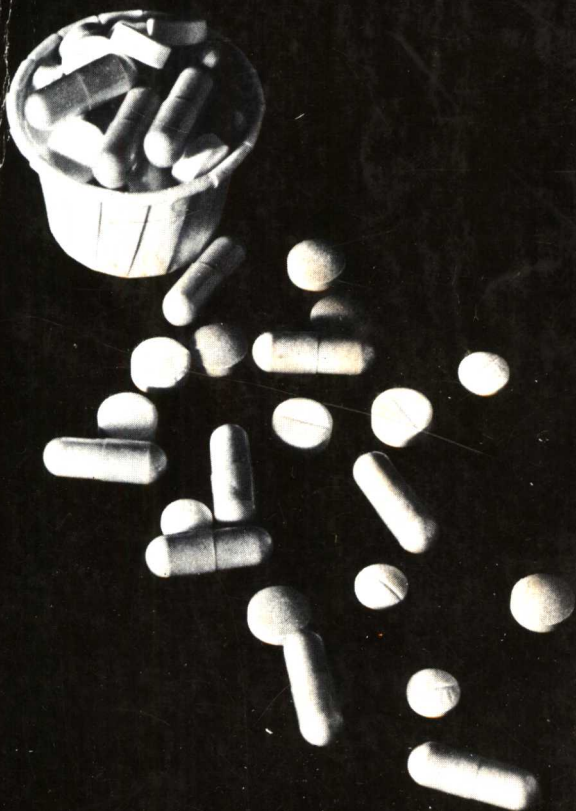
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*Handbook
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Preface

Proliferation of drug information represents only one aspect of the rapid growth of medical knowledge. Numerous studies of therapeutic indications, pharmacokinetics, and pharmacodynamics appear in the scientific literature and ultimately in textbooks, advertising literature, and circulars from drug information services and regulating agencies. However, this wealth of information often loses value by reason of its inaccessibility in circumstances of greatest relevance, such as in the assessment or treatment of a sick patient at the bedside or in the office.

Acutely aware of this difficulty and frustrated by the lack of a convenient source of "hard" data, we began to collect, evaluate, and tabulate the available data on commonly used drugs. The concept of this book was that it would be a readily available, informative source that would help solve many frequently posed problems, such as the adjustments of drug dosage in patients with renal and hepatic disease and the potential adverse effects and possible interactions of these drugs with other medications. Since we were then involved in research and were concerned with teaching clinical pharmacology and therapeutics to the medical and allied professions at the University of Kansas School of Medicine and at our home institutions, we believed it was also important to provide some relevant referencing of the primary literature for those seriously interested in gaining an in-depth knowledge of a particular drug. We trust that the description of each drug will answer most of the questions that are asked and that the references will permit the interested reader to evaluate related literature more easily. The chapters on the use of drugs in specific clinical conditions and age groups and on the definition of many of the terms commonly used in the clinical pharmacology literature should provide general background information and encourage more meaningful reading of the literature.

The fundamental goal of the book is the development of a critical and rational approach to the prescribing of drugs. It is commonly accepted that modern therapeutic efforts fall somewhat short of diagnostic accuracy, a failure that unfortunately may negate diagnostic excellence. We hope that this handbook will promote improved use of drugs through a better appreciation of their activity, and that the format of this text will lead to frequent, convenient consultation.

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Acknowledgments

Notice

The indications and dosages of all drugs in this *Handbook* have been recommended in the medical literature and conform to standards generally acceptable in medical practice. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contents

In the following list the terms given in capital letters are subtitles within this chapter.

*Not presently available in the United States.

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Do We Achieve
Rational Drug Therapy?

Daniel L. Azarnoff

It has been estimated that the cost of drugs was 9.3% of the $104.2 billion spent on health care in the United States in 1974 [8]. However, the percentage is greater, since unwarranted adverse reactions to drugs contribute to the cost included in the remaining 90%. Economic losses estimated in the billions of dollars due to illness and even death brought about by today's potent drugs add further to the expense.

Stedman's Medical Dictionary [21] defines rational therapy as a plan of treatment of disease based on the correct interpretation of the symptoms and a knowledge of the physiological action of the remedy. In other words, the physician must make the correct diagnosis and understand the pathophysiology of the disorder before deciding whether or not to treat a patient with a drug. If the answer is affirmative (and it definitely should not always be), the physician should know enough about drugs to select the right one and to administer it by the right route in the right amount at the right intervals for the right length of time. In addition, the physician must be aware of the potential for interactions with environmental, genetic, and disease-related factors. In general, physicians make the correct diagnosis with a reasonable degree of accuracy, but I am less sure that we are familiar with the pathophysiology of the disorder or the pharmacology of the drugs.

Irrational Drug Prescribing

Evidence of irrational prescribing by physicians is not difficult to find. Based on pharmaceutic production data, the consumption of prescription drugs in the United States has been estimated to have doubled over the past 10 years [20]. The average practitioner now writes about 8000 prescriptions per year. In 1975, greater than five prescriptions per capita were written in Australia, whereas from 1961 to 1971 approximately three per capita were written [24]. One must wonder if this 60% increase is the result of a more sickly population in 1975 or if the population is 60% or even 10% healthier as a result of increased drug usage. I doubt that either is true. In patients matched for age, sex, and illness, American physicians used almost 4 times as many drugs for the specific and nonspecific treatment of a variety of illnesses as did their Scottish counterparts [13]. As might be expected, the incidence of adverse effects was significantly higher in the American patients. Although it was not possible to obtain outcome results, there is no evidence that the Scottish patients were getting poorer care or were in poorer health. A review of prescribing

behavior revealed that two-thirds of all outpatient physician encounters resulted in the writing of at least one prescription [14]. We must ask ourselves whether these prescriptions were warranted or were used only to get rid of the patient. The ten most common indications for a prescription drug were insomnia, pain, constipation, anxiety, congestive heart failure, blood clotting, preoperative medication, bronchospasm, infection, and nausea. Described even in generous terms, we appear to be a nation of constipated, infected, wheezing, nauseated, anxious, thrombophlebitic insomniacs with failing hearts.

In an evaluation of physicians' prescribing habits, it was found that for more than 40% of prescriptions issued, the prescriber expected only a "hopeful" or "possible" value in patients with trivial conditions [15]. Greater than 90% of physicians in one community wrote one or more prescriptions for the common cold; 60% were for antibiotics or sulfonamides despite their known ineffectivness for this condition. Unwarranted and irrational use by physicians of dangerous drugs, such as chloramphenicol, has also been documented [18]. Even though safety may not be a factor, irrational prescribing has been documented in a study in which it was estimated that in Great Britain vitamin B_{12} usage was at least 4 times greater than the actual need [3]. Such irrational prescribing, if nothing else, adds to the cost of medical care.

Even after making the proper diagnosis and properly selecting and prescribing a drug, inadequate attention to the patient may still preclude satisfactory drug utilization. A significant number of patients never have their prescriptions filled and, even if they do, do not take the medication as directed by the physician [1]. At least in part, inadequate communication between the physician and patient is also responsible for this lack of compliance and breakdown in rational therapy.

Can physicians be utilizing drugs rationally when they continue to prescribe drugs in a manner that contradicts the current evidence? Why do the sales of sulfonylureas continue to rise when the University Group Diabetes Program (UGDP) study indicates they are of no benefit in the maturity onset diabetic and may hasten the onset of cardiovascular mortality [22]? Why are hormones still prescribed for the prevention of miscarriages or as a test for pregnancy despite the lack of evidence that they are effective for these indications and may produce birth defects [5, 9]? Why do we continue to prescribe clofibrate for the hyperlipidemic male patient with a previous myocardial infarction when this drug was demonstrated to be ineffective in preventing further cardiovascular morbidity and mortality in the Coronary Drug Project [4]? In fact, a significant increase in the incidence of thrombophlebitis, pulmonary embolus, and gallstones in patients receiving clofibrate was well documented in this study.

I believe we must conclude from these observations that drug therapy is not optimum. Rational drug therapy can no longer be based on a memorized schedule of dosage and contraindications. Drugs no longer are the herbals of yesteryear with questionable pharmacological activity; rather, they are potent chemicals with a potential for extensive harm as well as good. The practicing

physician is certainly not ignorant, negligent, nor unconcerned; he is busy and harried, working many hours per week. Importantly, however, he spends, on an average, less than 20 minutes a day reading the drug-related medical literature, which, unfortunately, is all too frequently inaccurate, irrelevant, unavailable, or misleading.

In considering the reasons for the lack of optimal drug therapy, we can classify drug-prescribing abuses [19] and perhaps identify the causes.

Overprescribing

Overprescribing exists when the drug is not needed or is given in a dose that is too large, for a period that is too long, or in a quantity that is too great for the patient's immediate needs. One cause of overprescribing is the use of drugs, such as sedatives, as a means of alleviating the patient's complaints when actually more complex solutions are required. The physician frequently uses the prescription as a means of terminating the visit. In a comparison of physicians and nurse practitioners it was found that after 1 year there was an increase in the use of vitamins and tonics (self-administered to some extent) in the physician-treated group of patients, whereas the use of tranquilizers and sedatives significantly decreased in the group followed by the nurses [2]. Could the difference be that the nurse practitioners took the time to talk to the patients?

Another cause of overprescribing is the desire to guarantee that everything possible that can be done has been done. This approach has been called by Kunin [11] the use of "drugs of fear," i.e., agents that help the physician resolve his own fear of failing to give the patient what he believes is the very best drug. Patients may also be responsible for the physician's overprescribing when they imply they have not received adequate attention unless they receive a prescription, or when they apply pressure to obtain a prescription that the physician would not ordinarily give. The prescribing of an antibiotic for a viral upper respiratory infection is a good example of this type of pressure. The physician assumes that, if he does not prescribe the antibiotic, the patient will go to another doctor who will prescribe it, so he may as well.

Underprescribing

Underprescribing is the failure to prescribe a required medication, such as a drug to lower blood pressure in a hypertensive patient. Inadequate dosage or administration for too brief a period also falls in this category. The reasons for this type of abuse include overemphasis on the risk of a useful drug, a skepticism about the efficacy of a drug for a particular indication, or a bad experience with a few patients in one's own practice.

Incorrect Prescribing

Incorrect prescribing occurs when the drug is given for the incorrect diagnosis, when the wrong drug is selected for the indication, or when the prescription is prepared improperly. Physicians' illegible handwriting is legendary.

Incorrect prescribing also occurs when a physician is not aware of or forgets that genetic and environmental factors or the disease per se may alter the patient's response to a drug. For example, cigarette-smoking may markedly accelerate the rate of elimination of a variety of drugs [17, 23]; low plasma albumin concentrations, as found in patients with the nephrotic syndrome, are associated with an increased fraction of unbound clofibrate and phenytoin, but the steady-state concentration of the unbound drug is not altered because of compensatory changes [7]; and downward dosage adjustments are necessary in patients with portacaval shunts who receive drugs with a significant first-pass effect [6].

An adverse response, such as a skin rash, is obvious to the physician and the patient, but the prevention of a satisfactory response, which is common, is much less readily discernible. Both may be the result of incorrect prescribing. For example, the "usual" dose of theophylline may not control bronchospasm in the patient who smokes due to induction of theophylline metabolism [10], whereas inhibition of phenytoin metabolism by isoniazid may result in ataxia in patients previously showing no signs of toxicity from the same dose. The latter is most likely to occur in patients who are slow acetylators of isoniazid [12]. In this instance, the drug interaction becomes clinically significant only in individuals with certain genetic determinants.

Multiple Prescribing

Abuses caused by multiple prescribing may occur when the patient visits and receives prescriptions from more than one physician, when the patient uses nonprescription drugs along with prescription drugs, or when the physician does not withdraw one drug before starting another or prescribes a brand-name product that contains several different drugs. In such instances the physician often forgets or is not aware that he is prescribing more than one active drug. The latter, as well as other examples, provides a cogent reason for prescribing only by generic name. If it is preferred or is necessary to prescribe a specific manufacturer's product, the generic name can be written first on the prescription, followed by that of the manufacturer.

Achieving Rational Drug Therapy

Today, healthy individuals as well as those who are chronically ill may receive drugs for long periods of time. Therefore, it behooves us to eliminate unwarranted drug utilization. What is required to accomplish this goal? I believe we need several approaches:

1   Improve and extend education about the rational use of drugs, starting in medical school and continuing throughout the practitioner's career. An educational program on rational uses of digitalis was undertaken for the house staff at a Montreal hospital. Simply emphasizing the importance of body weight and renal function when prescribing loading and maintenance doses of digoxin reduced the incidence of toxicity in this hospital from 21.4% to 12.3% over a 2-year period [16].

2   Reduce both the blatant and insidious pressures from patients and commercial sources that coerce the practitioner to increase drug utilization.

3   Provide sources of unbiased information about drugs.

4   Inculcate in the physician the realization that the selection and rational use of drugs is certainly as, and possibly even more, intellectually stimulating and rewarding than making the correct diagnosis.

Once the correct diagnosis is established, we must decide whether or not drug therapy is warranted. Frequently it is not. We must remember that the designation of a drug as safe and effective by a regulatory agency means only that the drug is statistically better than a placebo. *Statistically better* may mean better by only a few percentage points and be of little, if any, clinical consequence. Would you use a drug for a minor symptom if you knew the chance of producing a desirable effect was only 1 in 20? Some of us probably do.

Next we should set realistic goals by asking ourselves, "What am I trying to accomplish by administering this drug?" The goals should be both short- and long-term. For example, a short-term goal in treating diabetes mellitus would be control of the patient's blood sugar and a long-term goal would be prevention of retinopathy and nephropathy. End points should be defined to monitor both efficacy and toxicity. To do this, the relevant physiological, biochemical, behavioral, and physical characteristics should be measured at appropriate intervals. The patient's condition is not static. Therefore, we must continually review our treatment regimen and make any changes that are necessary by alterations in the patient's disease or response. All too often we prescribe a drug, such as digitalis for congestive heart failure, and years later the patient is still taking the drug at the same dosage originally prescribed. In the interim we have given little if any consideration to whether or not the use or initial dosage of this drug is still appropriate.

I have briefly set forth my views on the current status of drug therapy and made several broad suggestions for improvement. A major need is for nonbiased drug information. You may imagine my pleasure when the authors of this book informed me that they were gathering and critically reviewing the pharmacokinetic data available for many of the most commonly used drugs. As well-trained internists as well as clinical pharmacologists, Drs. Bochner, Carruthers, Kampmann, and Steiner are well qualified for this undertaking. For months I watched them put the information they gathered to use at the bedside of many patients. Soon it