General advice to prescribers

Rational approach to therapeutics

Drugs should only be prescribed when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risks involved. Bad prescribing habits lead to ineffective and unsafe treatment, exacerbation or prolongation of illness, distress and harm to the patient, and higher cost. The Guide to Good Prescribing. Geneva: WHO; 1994 provides undergraduates with important tools for training in the process of rational prescribing.

The following steps will help to remind prescribers of the rational approach to therapeutics.

1. **Define the patient's problem**

   Whenever possible, making the right diagnosis is based on integrating many pieces of information: the complaint as described by the patient; a detailed history; physical examination; laboratory tests; X-rays and other investigations. This will help in rational prescribing, always bearing in mind that diseases are evolutionary processes.

2. **Specify the therapeutic objective**

   Doctors must clearly state their therapeutic objectives based on the pathophysiology underlying the clinical situation. Very often physicians must select more than one therapeutic goal for each patient.

3. **Selecting therapeutic strategies**

   The selected strategy should be agreed with the patient; this agreement on outcome, and how it may be achieved, is termed concordance.

   The selected treatment can be non-pharmacological and/or pharmacological; it also needs to take into account the total cost of all therapeutic options.

   a. **Non-pharmacological treatment**

It is very important to bear in mind that the patient does not always need a drug for treatment of the condition. Very often, health problems can be resolved by a change in life style or diet, use of physiotherapy or exercise, provision of adequate psychological support, and other non–pharmacological treatments; these have the same importance as a prescription drug, and instructions must be written, explained and monitored in the same way.

b. **Pharmacological treatment**

- *Selecting the correct group of drugs*

  Knowledge about the pathophysiology involved in the clinical situation of each patient and the pharmacodynamics of the chosen group of drugs, are two of the fundamental principles for rational therapeutics.

- *Selecting the drug from the chosen group*

  The selection process must consider benefit/risk/cost information. This step is based on evidence about maximal clinical benefits of the drug for a given indication (efficacy) with the minimum production of adverse effects (safety).

  It must be remembered that each drug has adverse effects and it is estimated that up to 10% of hospital admissions in industrialized countries are due to adverse effects. Not all drug-induced injury can be prevented but much of it is caused by inappropriate selection of drugs.

  In cost comparisons between drugs, the cost of the total treatment and not only the unit cost of the drug must be considered.

- *Verifying the suitability of the chosen pharmaceutical treatment for each patient*

  The prescriber must check whether the active substance chosen, its dosage form, standard dosage schedule and standard duration of treatment are

suitable for each patient. Drug treatment should be individualized to the needs of each patient.

- *Prescription writing*

  The prescription is the link between the prescriber, the pharmacist (or dispenser) and the patient so it is important for the successful management of the presenting medical condition. This item is covered in more detail in the following section.

- *Giving information, instructions and warnings*

  This step is important to ensure patient adherence and is covered in detail in the following section.

- *Monitoring treatment*

  Evaluation of the follow up and the outcome of treatment allows the stopping of it (if the patient's problem is solved) or to reformulate it when necessary. This step gives rise to important information about the effects of drugs contributing to building up the body of knowledge of pharmacovigilance, needed to promote the rational use of drugs.

Variation in dose response

Success in drug treatment depends not only on the correct choice of drug but on the correct dose regimen. Unfortunately drug treatment frequently fails because the dose is too small or produces adverse effects because it is too large. This is because most texts, teachers and other drug information sources continue to recommend standard doses.

The concept of a standard or 'average' adult dose for every medicine is firmly rooted in the mind of most prescribers. After the initial 'dose ranging' studies on new drugs, manufacturers recommend a dosage that appears to produce the desired response in the majority of subjects. These studies are usually done on healthy, young male Caucasian volunteers, rather than on older men and women with illnesses and of different ethnic and environmental backgrounds. The use of standard doses in the marketing literature suggest that standard responses are the rule, but in reality there is considerable variation in drug response. There are many

reasons for this variation which include adherence (see below), drug formulation, body weight and age, composition, variation in absorption, distribution, metabolism and excretion, variation in pharmacodynamics, disease variables, genetic and environmental variables.

Drug formulation

Poorly formulated drugs may fail to disintegrate or to dissolve. Enteric-coated drugs are particularly problematic, and have been known to pass through the gastrointestinal tract intact. Some drugs like digoxin or phenytoin have a track record of formulation problems, and dissolution profiles can vary not only from manufacturer to manufacturer but from batch to batch of the same company. The problem is worse if there is a narrow therapeutic to toxic ratio, as changes in absorption can produce sudden changes in drug concentration. For such drugs quality control surveillance should be carried out.

Body weight and age

Although the concept of varying the dose with the body weight or age of children has a long tradition, adult doses have been assumed to be the same irrespective of size or shape. Yet adult weights vary two to threefold, while a large fat mass can store large excesses of highly lipid soluble drugs compared to lean patients of the same weight.

Age changes can also be important. Adolescents may oxidize some drugs relatively more rapidly than adults, while the elderly may have reduced renal function and eliminate some drugs more slowly.

DOSE CALCULATION IN CHILDREN

Children's doses may be calculated from adult doses by using age, body weight, or body surface area, or by a combination of these factors. The most reliable methods are those based on body surface area; these methods are used for calculating the doses of very toxic drugs.

Body weight may be used to calculate doses expressed in mg/kg. Young children may require a higher dose per kilogram than adults because of their proportionately higher metabolic capacity. Other problems need to be considered. For example, calculation by body weight in an obese child may result in much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age.

Body surface area (BSA) estimates are more accurate for calculation of paediatric doses than body weight because many physiological phenomena correlate better with body surface area. The average body surface area of a 70-kilogram human is about 1.8 m^2 . Thus, to calculate the dose for a child the following formula may be used:

$$\text{Approximate dose for patient} = \frac{\text{surface area of child } (m^2)}{1.8} \times \text{adult dose}$$

Nomograms are available to allow more precise body surface values to be calculated from a child's height and weight.

Where the dose for children is not readily available, prescribers should seek specialist advice before prescribing for a child.

Physiological and pharmacokinetic variables

Drug absorption rates may vary widely between individuals and in the same individual at different times and in different physiological states. Drugs taken after a meal are delivered to the small intestine much more slowly than in the fasting state, leading to much lower drug concentrations. In pregnancy gastric emptying is also delayed, while some drugs may increase or decrease gastric emptying and affect absorption of other drugs.

Drug distribution

Drug distribution varies widely: fat soluble drugs are stored in adipose tissue, water soluble drugs are distributed chiefly in the extracellular space, acidic drugs bind strongly to plasma albumin and basic drugs to muscle cells. Hence variation in plasma albumin levels, fat content or muscle mass may all contribute to dose variation. With very highly albumin bound drugs like warfarin, a small change of albumin concentration can produce a big change in free drug and a dramatic change in drug effect.

Drug metabolism and excretion

Drug metabolic rates are determined both by genetic and environmental factors. Drug acetylation shows genetic polymorphism, whereby individuals fall clearly into either fast or slow acetylator types. Drug oxidation, however, is polygenic, and although a small proportion of the population can be classified as very slow oxidizers of some drugs, for most drugs and most subjects there is a normal distribution of drug

metabolizing capacity, and much of the variation is under environmental control.

Many drugs are eliminated by the kidneys without being metabolized. Renal disease or toxicity of other drugs on the kidney can therefore slow excretion of some drugs.

Pharmacodynamic variables

There is significant variation in receptor response to some drugs, especially central nervous system responses, for example pain and sedation. Some of this is genetic, some due to tolerance, some due to interaction with other drugs and some due to addiction, for example, morphine and alcohol.

Disease variables

Both liver disease and kidney disease can have major effects on drug response, chiefly by the effect on metabolism and elimination respectively (increasing toxicity), but also by their effect on plasma albumin (increased free drug also increasing toxicity). Heart failure can also affect metabolism of drugs with rapid hepatic clearance (for example lidocaine, propranolol). Respiratory disease and hypothyroidism can both impair drug oxidation.

Enviromental variables

Many drugs and environmental toxins can induce the hepatic microsomal enzyme oxidizing system (MEOS) or cytochrome P450 oxygenases, leading to more rapid metabolism and elimination and ineffective treatment. Environmental pollutants, anaesthetic drugs and other compounds such as pesticides can also induce metabolism. Diet and nutritional status also impact on pharmacokinetics. For example in infantile malnutrition and in malnourished elderly populations drug oxidation rates are decreased, while high protein diets, charcoal cooked foods and certain other foods act as metabolizing enzyme inducers. Chronic alcohol use induces oxidation of other drugs, but in the presence of high circulating alcohol concentrations drug metabolism may be inhibited.

Adherence (compliance) with drug treatment

It is often assumed that once the appropriate drug is chosen, the prescription correctly written and the medication correctly dispensed, that

it will be taken correctly and treatment will be successful. Unfortunately this is very often not the case, and physicians overlook one of the most important reasons for treatment failure—poor adherence (compliance) with the treatment plan.

There are sometimes valid reasons for poor adherence—the drug may be poorly tolerated, may cause obvious adverse effects or may be prescribed in a toxic dose. Failure to adhere with such a prescription has been described as 'intelligent non-compliance'. Bad prescribing or a dispensing error may also create a problem, which patients may have neither the insight nor the courage to question. Even with good prescribing, failure to adhere to treatment is common. Factors may be related to the patient, the disease, the doctor, the prescription, the pharmacist or the health system and can often be avoided.

Low-cost strategies for improving adherence increase effectiveness of health interventions and reduce costs. Such strategies must be tailored to the individual patient.

Health care providers should be familiar with techniques for improving adherence and they should employ systems to assess adherence and to determine what influences it.

Patient reasons

In general, women tend to be more adherent than men, younger patients and the very elderly are less adherent, and people living alone are less adherent than those with partners or spouses. Specific education interventions have been shown to improve adherence. Patient disadvantages such as illiteracy, poor eyesight or cultural attitudes (for example preference for traditional or alternative medicines and suspicion of modern medicine) may be very important in some individuals or societies; as may economic factors. Such disabilities or attitudes need to be discussed and taken account of.

Disease reasons

Conditions with a known worse prognosis (for example cancer) or painful conditions (for example rheumatoid arthritis) elicit better adherence rates than asymptomatic 'perceived as benign' conditions such as hypertension. Doctors should be aware that in most settings less than half of patients initiated on antihypertensive drug treatment are still taking it a year later. Similarly, in epilepsy, where events may occur at long intervals, adherence is notoriously unsatisfactory.

Doctor reasons

Doctors may cause poor adherence in many ways—by failing to inspire confidence in the treatment offered, by giving too little or no explanation, by thoughtlessly prescribing too many medicines, by making errors in prescribing, or by their overall attitude to the patient.

The doctor-patient interaction

There is considerable evidence that this is crucial to concordance. 'Satisfaction with the interview' is one of the best predictors of good adherence. Patients are often well informed and expect a greater say in their health care. If they are in doubt or dissatisfied they may turn to alternative options, including 'complementary medicine'. There is no doubt that the drug 'doctor' has a powerful effect to encourage confidence and perhaps contribute directly to the healing process.

Prescription reasons

Many aspects of the prescription may lead to non-adherence (non-compliance). It may be illegible or inaccurate; it may get lost; it may not be refilled as intended or instructed for a chronic disease. Also, the prescription may be too complex; it has been shown that the greater the number of medications the poorer the adherence, while multiple doses also decrease adherence if more than two doses per day are given. Not surprisingly adverse effects like drowsiness, impotence or nausea reduce adherence and patients may not admit to the problem.

Pharmacist reasons

The pharmacist's manner and professionalism, like the doctor's, may have a positive impact, supporting adherence, or a negative one, raising suspicions or concerns. This has been reported in relation to generic drugs when substituted for brand-name drugs. Pharmacist information and advice can be a valuable reinforcement, as long as it agrees with the doctor's advice.

The health care system

The health care system may be the biggest hindrance to adherence. Long waiting times, uncaring staff, uncomfortable environment, exhausted drug supplies and so on, are all common problems in developing countries, and have a major impact on adherence. An important problem is the distance and accessibility of the clinic from the patient. Some studies have

confirmed the obvious, that patients furthest from the clinic are least likely to adhere to treatment in the long term.

Recommendations

- Review the prescription to make sure it is correct.
- Spend time explaining the health problem and the reason for the drug.
- Establish good rapport with the patient.
- Explore problems, for example difficulty with reading the label or getting the prescription filled.
- Encourage patients to bring their medication to the clinic, so that tablet counts can be done to monitor compliance.
- Encourage patients to learn the names of their medicines, and review their regimen with them. Write notes for them.
- Keep treatment regimens simple.
- Communicate with other health care professionals, to develop a team approach and to collaborate on helping and advising the patient.
- Involve the partner or another family member.
- Listen to the patient.

Adverse effects and interactions

Adverse drug reactions

An adverse drug reaction (ADR) may be defined as 'any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis, or therapy...'. ADRs are therefore unwanted or unintended effects of a medicine, including idiosyncratic effects, which occur during its proper use. They differ from accidental or deliberate excessive dosage or drug maladministration, (see section 4 for the treatment of poisoning).

ADRs may be directly linked to the properties of the drug in use, the so-called 'A' type reactions. An example is hypoglycaemia induced by an antidiabetic drug. ADRs may also be unrelated to the known pharmacology of the drug, the 'B' type reactions including allergic effects, for example anaphylaxis with **penicillins** .

Thalidomide marked the first recognized public health disaster related to the introduction of a new drug. It is now recognized that clinical trials, however thorough, cannot be guaranteed to detect all adverse effects likely to be caused by a drug. Health workers are thus encouraged to

record and report to their national pharmacovigilance centre any unexpected adverse effects with any drug to achieve faster recognition of serious related problems. For example, from reports received in one country, a relationship was established between **thioacetazone** and Stevens-Johnson syndrome when the drug was used in HIV infection, leading to the withdrawal of the drug in that country.

Major factors predisposing to adverse effects

It is well known that different patients often respond differently to a given treatment regimen. For example, in a sample of 2422 patients who had been taking combinations of drugs known to interact, only 7 (0.3%) showed any clinical evidence of interactions. In addition to the pharmaceutical properties of the drug therefore, there are characteristics of the patient which predispose to ADRs.

EXTREMES OF AGE

The very old and the very young are more susceptible to ADRs. Drugs which commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal anti-inflammatory drugs, antihypertensives, psychotropics and digoxin.

All children, and particularly neonates, differ from adults in their response to drugs. Some drugs are likely to cause problems in neonates (for example **morphine**), but are generally tolerated in children. Other drugs (for example **valproic acid**) are associated with increased risk of ADRs in children of all ages. Other drugs associated with problems in children include **chloramphenicol** (grey baby syndrome), **antiarrhythmics** (worsening of arrhythmias), **acetylsalicylic acid** (Reye syndrome).

INTERCURRENT ILLNESS

If besides the condition being treated the patient suffers from another disease, such as kidney, liver or heart disease, special precautions may be necessary to prevent ADRs. Remember also that, as well as the above factors, the genetic make-up of the individual patient may predispose to ADRs.

DRUG INTERACTIONS

Interactions (see also Appendix 1) may occur between drugs which compete for the same receptor or act on the same physiological system.

They may also occur indirectly when a drug-induced disease or a change in fluid or electrolyte balance alters the response to another drug.

Interactions may occur when one drug alters the absorption, distribution or elimination of another drug, such that the amount which reaches the site of action is increased or decreased.

Drug-drug interactions are some of the commonest causes of adverse effects. When two drugs are administered to a patient, they may either act independently of each other, or interact with each other. Interaction may increase or decrease the effects of the drugs concerned and may cause unexpected toxicity. As newer and more potent drugs become available, the number of serious drug interactions is likely to increase. Remember that interactions which modify the effects of a drug may involve non-prescription drugs, non-medicinal chemical agents, and social drugs such as **alcohol** , **marijuana** , **tobacco** , **and traditional remedies** , as well as certain types of food for example grapefruit juice. The physiological changes in individual patients, caused by such factors as age and gender, also influence the predisposition to ADRs resulting from drug interactions.

The following table lists drugs under the designation of specific cytochrome P450 isoforms. A drug appears in a column if there is published evidence that it is metabolized, at least in part, via that isoform. Alterations in the rate of the metabolic reaction catalyzed by that isoform are likely to have effects on the pharmacokinetics of the drug.

Cytochrome P450 Drug Interaction Table

		SUBSTRATES			
CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP2D6	C
Theophylline	Cyclophosphamide	Amitriptyline	Ibuprofen	Amitriptyline	A
	Efavirenz	Clomipramine	Phenytoin	Clomipramine	P
		Cyclophosphamide	Sulfamethoxazole	Codeine	
		Diazepam	Tamoxifen	Haloperidol	
		Phenobarbital	Warfarin	Tamoxifen	
		Phenytoin		Timolol	

			INHIBITORS		
1A2	2B6	2C19	2C9	2D6	2I
Ciprofloxacin			Isoniazid	Chlorphenamine Clomipramine Haloperidol Quinidine Ritonavir	
			INDUCERS		
1A2	2B6	2C19	2C9	2D6	2I
Tobacco	Phenobarbital Rifampicin		Rifampicin		A Is

Incompatibilities between drugs and intravenous fluids

Drugs should not be added to blood, amino acid solutions or fat emulsions. Certain drugs, when added to intravenous fluids, may be inactivated by pH changes, by precipitation or by chemical reaction. **Benzylpenicillin** and **ampicillin** lose potency after 6–8 hours if added to dextrose solutions, due to the acidity of these solutions. Some drugs bind to plastic containers and tubing, for example **diazepam** and **insulin** . **Aminoglycosides** are incompatible with **penicillins** and **heparin** . **Hydrocortisone** is incompatible with **heparin** , **tetracycline** , and **chloramphenicol** .

Adverse effects caused by traditional medicines

Patients who have been or are taking traditional herbal remedies may develop ADRs. It is not always easy to identify the responsible plant or plant constituent. Refer to the drug and toxicology information service if available and/or to suitable literature.

The effect of food on drug absorption

Food delays gastric emptying and reduces the rate of absorption of many drugs; the total amount of drug absorbed may or may not be reduced. However, some drugs are preferably taken with food, either to increase absorption or to decrease the irritant effect on the stomach.

Prescription writing

A prescription is an instruction from a prescriber to a dispenser. The prescriber is not always a doctor but can also be a paramedical worker, such as a medical assistant, a midwife or a nurse. The dispenser is not always a pharmacist, but can be a pharmacy technician, an assistant or a nurse. Every country has its own standards for the minimum information required for a prescription, and its own laws and regulations to define which drugs require a prescription and who is entitled to write it. Many countries have separate regulations for prescriptions for controlled drugs such as opioid analgesics.

The following guidelines will help to ensure that prescriptions are correctly interpreted and leave no doubt about the intention of the prescriber. The guidelines are relevant for primary care prescribing; they may, however, be adapted for use in hospitals or other specialist units.

Prescription form

The most important requirement is that the prescription be clear. It should be legible and indicate precisely what should be given. The local language is preferred.

The following details should be shown on the form:

- The prescriber's name, address and telephone number. This will allow either the patient or the dispenser to contact the prescriber for any clarification or potential problem with the prescription.
- Date of the prescription. In many countries the validity of a prescription has no time limit, but in some countries pharmacists do not dispense drugs on prescriptions older than 3 to 6 months.
- Name, form and strength of the drug. The International Nonproprietary Name of the drug should always be used. If there is a specific reason to prescribe a special brand, the trade name can be added. Generic substitution is allowed in some countries. The pharmaceutical form (for example 'tablet', 'oral solution', 'eye ointment') should also be stated.
- The strength of the drug should be stated in standard units using abbreviations that are consistent with the Système Internationale (SI). 'Microgram' and 'nanogram' should not, however, be abbreviated. Also, 'units' should not be abbreviated. Avoid decimals whenever possible. If unavoidable, a zero should be written in front of the decimal point.

- Specific areas for filling in details about the patient including name, address and age.

Directions

Directions specifying the route, dose and frequency should be clear and explicit; use of phrases such as ‘take as directed’ or ‘take as before’ should be **avoided** .

For preparations which are to be taken on an ‘as required’ basis, the minimum dose interval should be stated together with, where relevant, the maximum daily dose. It is good practice to qualify such prescriptions with the purpose of the medication (for example ‘every 6 hours as required for pain’, ‘at night as required to sleep’).

It is good practice to explain the directions to the patient; these directions will then be reinforced by the label on the medicinal product and possibly by appropriate counselling by the dispenser. It may be worthwhile giving a written note for complicated regimens although it must be borne in mind that the patient may lose the separate note.

Quantity to be dispensed

The quantity of the medicinal product to be supplied should be stated such that it is not confused with either the strength of the product or the dosage directions.

Alternatively, the length of the treatment course may be stated (for example ‘for 5 days’).

Wherever possible, the quantity should be adjusted to match the pack sizes available.

For liquid preparations, the quantity should be stated in millilitres (abbreviated as ‘ml’) or litres (preferably not abbreviated since the letter ‘l’ could be confused with the figure ‘1’).

Narcotics and controlled substances

The prescribing of a medicinal product that is liable to abuse requires special attention and may be subject to specific statutory requirements. Practitioners may need to be authorized to prescribe controlled substances; in such cases it might be necessary to indicate details of the authority on the prescription.

In particular, the strength, directions and the quantity of the controlled substance to be dispensed should be stated clearly, with all quantities written in words as well as in figures to prevent alteration. Other details such as patient particulars and date should also be filled in carefully to avoid alteration.

Sample prescription

PRESCRIPTION

Dr B Who
Geneva
Switzerland
Tel: 791 2111

Date: _____

Name of patient _____

Address _____

_____

_____

Date of birth _____ Sex _____

℞

For use by the dispensary