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Rational prescribing: the principles of drug selection

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Prescribing is a complex task requiring:

- diagnostic skills
- knowledge of medicines
- an understanding of the principles of clinical pharmacology
- communication skills
- appreciation of risk and uncertainty.

The accumulation of clinical trials' data on modern therapies might have been expected to provide sufficient evidence to support most clinical decisions. In fact, clinicians prescribe in varied circumstances, often in the absence of evidence, and rational prescribing decisions must be based on knowledge interpreted in the light of many other factors.

Rational prescribing

Rational prescribers should attempt to:

- maximise clinical effectiveness
- minimise harms
- avoid wasting scarce healthcare resources
- respect patient choice.

Rational prescribing normally follows a logical sequence from diagnosis to follow-up (Fig 1).

Diagnosis

Prescribing decisions should be based on the primary diagnosis and relevant secondary diagnoses. Ideally, these should have been made or confirmed by the prescriber who will take responsibility for the effects of treatment. Appreciating that diagnoses are made with varying degrees of uncertainty is important when assessing the benefit-to-harm balance of treatment. For instance, antibiotics are often prescribed on the basis of presumed antibacterial sensitivity with the expectation of significant benefit. However, this can expose the recipient to harm without the prospect of cure.

Prognosis

The prognoses of the primary and secondary diagnoses will affect rational treatment choices. A secondary diagnosis with a poor prognosis, such as lung cancer, will severely limit the benefits of treating a primary one, such as hypercholesterolaemia. On the other hand, the excellent prognosis of influenza in a healthy adult limits the potential benefits of antiviral therapy.

Goals of therapy

Goals of therapy may include:

- curing a disease (eg cancer, infection)
- relieving symptoms without affecting the underlying condition (eg headache, diarrhoea)
- combining two outcomes (eg inflammatory bowel disease and arthritis)
- long-term prevention (eg hypertension, osteoporosis)
- replacing deficiencies (eg hypothyroidism), and occasionally
- therapeutic trials to aid diagnosis.

Treatment selection

Prescribers are commonly faced with more than one choice of treatment, including non-pharmacological therapies or no treatment. For example, the management of arthritis might include reassurance, simple analgesia, physiotherapy, non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, intra-articular steroids or surgery.

Monitoring

Each prescription constitutes an experiment the outcome of which is never certain. It is therefore important to monitor the effects of treatment, re-evaluate the benefit-harm balance and, if indicated, withdraw the drug or change the dose. The most appropriate end-point will be objective assessment of the clinical outcome (eg recovery from pneumonia), but assessment may be subjective (eg pain relief, improved quality of life). Patient satisfaction is also important. Sometimes

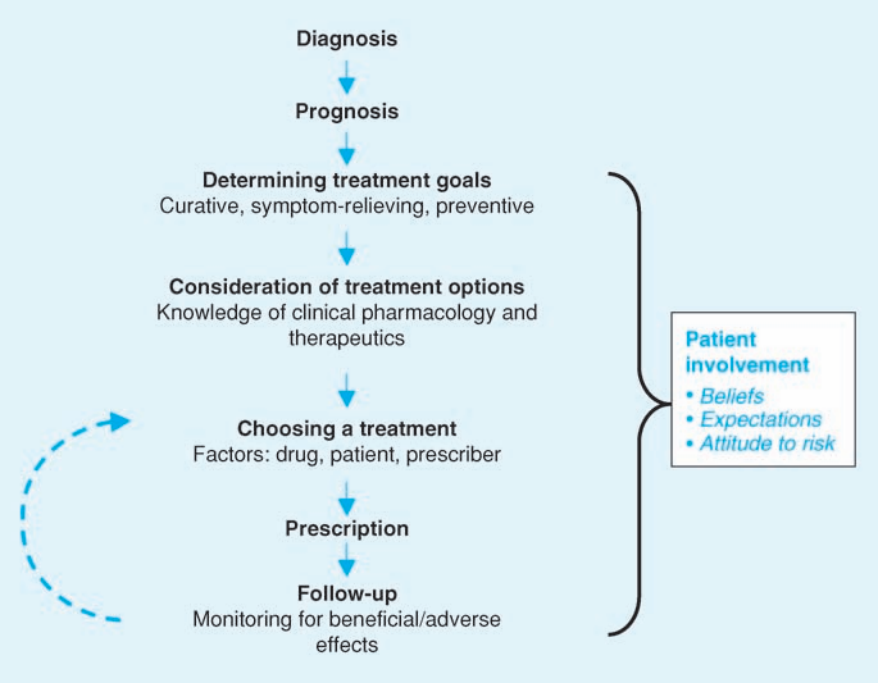

Fig 1. The process of rational prescribing.

the outcome is difficult to measure (eg management of epilepsy) or requires long-term follow-up (eg preservation of health in HIV infection). In such cases, validated surrogate markers (eg serum anticonvulsant concentration, CD4 cell count) may guide therapy. Adverse events can also be monitored in different ways.

Partnership with patients

Patients make important contributions to rational prescribing decisions. Their beliefs and expectations affect the goals of therapy and help in judging the acceptable benefit-harm balance when selecting treatments. They will often play a key role in monitoring treatment, not least by providing early warning of adverse events. Patients involved in clear communication with prescribers concerning reasons for drug selection, goals, duration of treatment and potential adverse effects have improved compliance, more confidence in prescribers and greater satisfaction with healthcare services. Thus, whenever possible, patients should be fully informed about their medicines (Table 1).

Drug and dose selection

Having considered diagnosis, prognosis and goals of therapy, prescribers often select from several pharmacological options. The best choice should maximise the benefit-harm balance based on drug and patient factors, taking into account restrictions based on availability and costs (Table 2).

Table 1. What patients need to know about their medicines.

- The reason for taking the medicine
- How the medicine works
- How to take the medicine
- What benefits to expect (how to know if it works)
- What adverse effects might occur:
  - common
  - serious
- Precautions that improve safety:
  - symptoms to report
  - monitoring required
  - potential drug-drug interactions
- When to return for review

Drug factors influencing drug selection

Pharmacokinetics

Drugs in the same class (or different formulations of the same drug) may have different bioavailability, dose-concentration curves and half-lives. These factors will determine the dosing schedule. Once-daily dosing is convenient and encourages adherence. Pharmacokinetic characteristics may also influence interindividual variability in dosage requirements. For example, some drugs:

- differ with respect to their specificity for the target organ
- reach tissues (eg the brain) to cause adverse effects
- are metabolised in the liver or excreted – important in patients with hepatic or renal impairment
- are more likely to cause drug interactions by cytochrome P450 inhibition (eg simvastatin versus pravastatin).

Pharmacodynamics

A drug with a low therapeutic index (the ratio between the dose required to cause adverse effects and that required for efficacy) is less favourable if alternatives exist. Similarly, the steepness of the dose-response curve will influence the ease with which the dose can be optimally titrated. Selectivity for a receptor subtype may be relevant when choosing drugs

Table 2. Factors that influence rational drug and dosage selection.

Diagnosis	Primary: condition to be treated Secondary: other conditions that may influence the benefit-to-harm balance
Prognosis	Influences the likely duration of benefits and harms of treatment
Drug factors:	
Pharmacokinetic	Frequency of dosing: influences adherence Bioavailability: if consistent, makes drug response more predictable Tissue distribution: can affect adverse effects at sites other than targeted Routes of metabolism/excretion: increased anticipation of variable response Drug interactions: greater safety if less frequent
Pharmacodynamic	Target specificity and selectivity: influences likelihood of adverse effects Dose-response characteristics: influences ease of dose titration Therapeutic index: influences ease of dose selection
Therapeutic	Efficacy in relieving symptoms Efficacy on morbidity/mortality/hospitalisation Impact on disease progression (eg prolongation of life)
Safety	Frequency of adverse effects Seriousness of adverse effects (eg allergy, idiosyncratic reactions) Ease with which adverse effects can be predicted, monitored and prevented
Cost	Availability of alternatives with similar efficacy
Patient factors	Health beliefs and attitude to risk History of previous adverse drug reactions Vulnerability to adverse effects (eg organ damage, reduced physiological reserve) Current drug therapy including interacting drugs Likely adherence to therapy or follow-up monitoring
Prescriber factors	Familiarity with prescribing choices Ease of follow-up: may depend on resources

that avoid predictable adverse effects. Some drugs require more complex monitoring, which can affect costs and patient time (eg warfarin versus aspirin).

Therapeutic impact and safety

A drug may be more efficacious in relieving symptoms, improving surrogate markers or preventing clinical events (eg morbidity, mortality, hospitalisation) or have fewer and less serious adverse effects (eg carbamazepine *v* phenytoin). Large randomised controlled trials (RCTs) are considered the optimal sources of evidence, but extrapolating the results to prescribing decisions in the real world requires caution. RCTs usually recruit highly selected participants (eg based on age or disease severity) without comorbidities or receiving interacting drugs. Such additional factors can influence efficacy or adverse outcomes, potentially reducing the former and enhancing the latter, thus limiting the external validity of RCTs.

Costs

All healthcare systems have limited resources. The rapidly increasing cost of medicines forces all prescribers to consider cost-effectiveness as a factor in drug selection. This is taken into account when devising local formularies and in the decisions of the National Institute for Health and Clinical Excellence. Perhaps the most obvious example of cost-effective prescribing is selecting a generic rather than a branded drug from the same class. However, cost may be outweighed by other factors, notably significant differences in efficacy or safety. (See accompanying article on pharmacoeconomics.)

Patient factors influencing drug selection

Previous adverse drug reactions

Knowledge of previous adverse reactions will affect drug or dose selection but depends on taking a careful drug history. This is particularly important in the case of allergic reactions (eg beta-lactam antibiotics).

Vulnerability to adverse effects

Some patients will have organ damage that may affect drug choices. For instance, a beta-blocker for angina may be undesirable in patients with peripheral vascular disease or asthma but attractive in those with heart failure. Reduced physiological reserve increases the vulnerability of elderly patients to the adverse effects of many drugs (eg anticholinergics, central nervous system depressants, vasoactive drugs) and necessitates dosage reductions.

Current drug therapy

Any current drug therapy may affect drug or dosage selection, mainly because of potential drug interactions. For example, the dose of simvastatin should not be increased beyond 20 mg nocte in patients taking amiodarone or verapamil because of the increased risk of muscle toxicity.

Other patient factors

The likelihood that patients will adhere to therapy or follow-up monitoring is important for drugs such as warfarin and insulin which have a low therapeutic index and where alternatives are less effective. Health beliefs and attitude to risk can influence the initial decision to prescribe or the choice of medicine. This is particularly obvious in long-term preventive therapy when benefits may be imperceptible. About half of patients adhere poorly to such treatments, emphasising the role of patient partnership in making rational prescribing decisions.

Prescriber factors influencing drug selection

Familiarity

Lack of familiarity of prescribers with medicines increases the chance of adverse outcomes, mandating continuing professional development. However, lack of experience should not impede the introduction of new, more rational prescribing practices.

Ease of follow-up

Some medicines require careful review and monitoring to ensure that safety is maximised or dose titration optimal. The ease with which these can be accomplished is important.

Examples of irrational prescribing

Rational prescribing aims to ensure that selection is not a simple formulaic linkage of drugs and doses to particular diagnoses, but involves individualising prescriptions as far as possible, taking account of the variables discussed above.

Table 3 offers some simple examples of irrational prescribing. They are illustrative only and do not acknowledge the complexity of real prescribing decisions. Prescribers commonly make probabilistic judgements that involve interpreting trial evidence in the light of specific circumstances such as patients' wishes, availability of resources and previous adverse events. For instance, more

Key Points

- **Prescribing is a complex task that requires interpretation of evidence from clinical trials in light of individual patient factors**
- **Rational prescribing describes a logical approach that includes making a diagnosis, estimating prognosis, establishing the goals of therapy, selecting the most appropriate treatment and monitoring the effects of the treatment**
- **Patients should be involved in several of these stages and their beliefs, expectations and attitudes to risk will contribute to rational prescribing decisions**
- **Pharmacogenetics will help to individualise prescribing choices but will not replace the need for an understanding of the clinical pharmacology underpinning the selection of commonly prescribed drugs**

KEY WORDS: drug selection, interindividual variation, monitoring therapy, rational prescribing

expensive but equivalent medications may be justified if others have caused adverse effects or loss of confidence. Higher risk medicines may be acceptable if the potential benefit is estimated to be greater for an individual patient.

Personalised medicines: the future?

This article has discussed the traditional approach to prescribing in which individualised drug selection is based on evidence gathered from groups of similar patients mixed with best-guess judgements about the variability introduced by specific patient and drug factors. Recently, a new era of 'personalised' treatment has been predicted in which therapeutic choices will be individualised based on genetic variables affecting drug handling and action, allowing more specific prediction of outcomes. Indeed, pharmacogenetics is already being used to distinguish responders from non-responders (eg trastuzumab for HER2-overexpressing breast cancer) and to avoid adverse effects (eg HLA B*5701 for abacavir hypersensitivity). (See accompanying article on pharmacogenetics.)

The impact of this approach may however be limited because many of the variables outlined in Table 2 are not affected by genetics. This suggests that rational prescribing will remain based on a firm grounding in the principles of clinical pharmacology.

Further reading

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Table 3. Examples of irrational prescribing.

Reason	Example
Low chance of benefit (compared with harm):	
Short-term conditions with good prognosis	Antiviral drugs for influenza in healthy adults
Preventive therapy in patients with poor prognosis conditions/poor quality of life	Statin therapy in patients with a malignancy
Drugs used beyond the evidence base	Statin therapy for very young or very old patients
Dose too low	ACEIs for CHF
Wrong diagnosis	Anti-anginal drugs prescribed for patients with GOR
	Antibiotics for viral illnesses
Increased risk of harm (compared with benefit):	
Vulnerability to adverse effects	Prescribing psychoactive medicines for elderly patient; NSAIDs for patients with impaired renal function; thromboprophylaxis in patients at risk of serious bleeding due to factors such as thrombocytopenia, peptic ulcer disease, coagulopathies, intracranial disease
Drug clearance altered	Wrong doses in patients with renal or hepatic disease
Drug interactions likely	Enzyme-inhibiting drugs in patients taking warfarin
Dose too high	Thiazide diuretics as antihypertensives
	Aspirin for the prevention of cardiovascular disease
Reduced adherence likely:	
Too many medicines (polypharmacy) in patients with multiple conditions	Prescribing all evidence-based therapies in elderly patients with chronic airways disease, hypertension, CHF, osteoporosis, GOR or RA
Poor communication	Antihypertensive drugs in young patients unclear about or unimpressed with the extent of likely benefit
Unnecessary cost:	
Expensive drugs with no evidence of superior outcomes when cheaper drugs exist	Prescribing branded rather than generic statins in primary prevention
Expensive drugs that offer slightly better outcomes at enormously increased cost	Some new therapies for cancer
Drugs for ADRs:	
Drugs prescribed to counteract the adverse effects of other medicines that could be replaced with suitable alternatives	Laxatives for verapamil-induced constipation Salbutamol for beta-blocker-induced bronchospasm Diuretics for amlodipine-induced ankle oedema

ACEI = angiotensin-converting enzyme inhibitor; ADR = adverse drug reaction; CHF = chronic heart failure; GOR = gastro-oesophageal reflux; NSAID = non-steroidal anti-inflammatory drug; RA = rheumatoid arthritis.

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