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Rational prescribing: the principles of drug selection and assessment of efficacy

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Most experienced prescribers believe that the principles of rational prescribing underpin their choice of therapy. However, without a robust understanding of the basis for decisions, drug choice can become formulaic and ignore individual patient variability. Rational prescribing should:

- maximise effectiveness
- minimise risks
- respect patient choice, and
- minimise costs.

A logical sequence of events usually precedes a rational prescription, comprising:

- making a diagnosis (or differential diagnoses)
- determining the prognosis of the condition to be treated
- determining the goal(s) of treatment (eg curative, symptom-relieving, preventive or, occasionally, an aid to the diagnostic process), and
- selecting an appropriate type of treatment.

It is unusual for only one treatment option to be available and a selection is made from a range of possible approaches. For example, an explanation may be sufficient to satisfy a patient with brief, infrequent episodes of supraventricular tachycardia. For longer episodes, vagotonic manoeuvres may terminate the symptoms. More frequent or symptomatic tachycardias may be suppressed by a beta-blocker or calcium channel antagonist, and it may also be appropriate to consider an electrophysiological study with a view to ablation of the originating focus.

Evidence from large-scale randomised controlled trials (RCTs) is often used to guide the choice of treatment. However, many assumptions are made when extrapolating evidence from a highly selected population sample to general clinical practice, ignoring exclusion criteria that were applied during recruitment. A drug that is superior in clinical trials may prove less effective in clinical practice because of variability in individual responses or be less suitable for an individual because of potential adverse effects. In the former situation, there is no reliable way to determine the probability of a successful outcome in an individual; in the latter, good clinical judgement should override the results of clinical trials.

Assessing treatment outcomes

When a drug is chosen as part of the therapeutic strategy, it is important to monitor the outcome of that choice. Measuring the desired therapeutic effect may seem intuitive, but is often elusive. The ideal end-point will be a relevant clinical outcome, determined by an objective measure, such as survival after antibiotic treatment for meningococcal septicaemia, control of ventricular rate in atrial fibrillation or the frequency of symptoms in angina. Often, the end-point will be subjective, such as relief of pain in arthritis or the ability to perform activities of daily living in Parkinson's disease. In clinical trials, such subjective outcomes will be measured with a validated tool such as a visual analogue scale or a quality-of-life questionnaire. In clinical practice, patient satisfaction with the prescribed treatment will be the usual criterion of success.

Surrogate end-points

Surrogate end-points can be a valid and useful outcome measure if the effect of an intervention on the surrogate end-point fully predicts the effect on the desired clinical outcome. However, they

may still fail to predict the actual consequences of treatment, even though they are a correlate of the true clinical outcome, and are likely to be valid only if the surrogate is a part of the causal pathway of the disease process. Examples of surrogate end-points that appear to be reliable predictors of outcome include the effect of insulin therapy on blood glucose in diabetes mellitus (predicting the risk of certain diabetic complications) and the effect of allopurinol on plasma uric acid (predicting the reduction in the risk of an acute attack of gout).

Some notable surrogates that have failed to predict subsequent mortality include suppression of ventricular ectopics after myocardial infarction (MI) by antiarrhythmic drugs, the response of tumour markers to drug therapy in cancer, and the response of the CD4 cell count to drug therapy in HIV infection.

Population studies

The efficacy of preventive or prophylactic therapies can be assessed only in population studies. The apparent efficacy of a drug in such studies can be applied to an individual in clinical practice only in terms of a statistical probability of preventing an undesirable outcome. Most preventive treatments reduce but do not eliminate the risk of an undesirable outcome. Taking a statin reduces the risk of an MI but many individuals will still eventually experience an event despite treatment.

Individualising drug therapy

If a decision is taken to give drug therapy, a number of aspects should be considered by the prescriber (Table 1). Judicious prescribing, with consideration of comorbidities, will sometimes allow simplification of a drug regimen. For example, in a person with hypertension controlled by a thiazide diuretic who develops angina, substitution of a calcium channel antagonist for the diuretic, rather than adding the calcium channel antagonist or using a long-acting nitrate, may permit symptom relief while maintaining optimal blood pressure control.

Addition of a new treatment to existing treatments may make a previous drug redundant and the need for continued use of each drug should be regularly reviewed. A good example is the treatment of chronic heart failure. Initially, intensive therapy with a loop diuretic may be essential to treat fluid overload. However, once the condition has been stabilised with full doses of an angiotensin-converting enzyme inhibitor (ACEI), a beta-blocker and perhaps spironolactone, the loop diuretic may become redundant and can often be gradually withdrawn without clinical deterioration. Indeed, continuing treatment may lead to dehydration, electrolyte disturbance, renal impairment and troublesome hypotension. At this point, the risks of continuing treatment far outweigh any benefits.

When is prescribing not rational?

Polypharmacy

Many medical conditions require treatment with several drugs to achieve an optimal outcome. An example is the use of aspirin, clopidogrel, a statin, an ACEI and a beta-blocker after a non-ST elevation MI. Each drug has evidence from RCTs for a reduction in subsequent re infarction and risk of death; the effects

Key Points

Rational prescribing should maximise effectiveness, minimise risks, respect patient choice and minimise costs

A drug that is superior in clinical trials may prove less effective in clinical practice

It is important to monitor the outcome of treatment using an objective measure

Surrogate end-points can be valid and useful if they are part of the causal pathway of the disease process

There should be individualised therapy as far as possible, taking into account any comorbidities, contraindications and coexisting medication

Unnecessary polypharmacy and unnecessarily expensive drugs should be avoided

Patients should be involved in their treatment by being told the reason for it, its likely effect, how it should be taken and for how long

KEY WORDS: end-points, individualisation, monitoring, rational prescribing, treatment outcomes

Table 1. Aspects to be considered before giving drug therapy.

- Understand how the proposed drug compares with available alternatives in published evidence of efficacy, adverse effects, convenience and cost
- Individualise therapy as far as possible
- Determine an appropriate dosage regimen for efficacy and convenience (once or twice daily dosing encourages adherence)
- Determine any contraindications to using the drug in this individual, including comorbidities or common adverse effects
- Consider potential drug interactions
- Have a clear goal for treatment and decide how and when to assess therapeutic response or monitor for potential adverse effects
- Plan dosage titration, the appropriate maximum dosage and the proposed duration of treatment at the outset
- Have a contingency plan for therapeutic failure or adverse effects

are believed to be additive. However, unnecessary polypharmacy is irrational and often arises by default rather than by intent. In the example given above, there is no evidence that the use of clopidogrel beyond one year will confer additional benefit. Continuing treatment beyond this time is not rational on the basis of the current evidence.

Side effects

Using a drug to counteract a side effect of another drug is not always rational if an alternative drug could be substituted for the original agent. If verapamil causes troublesome constipation, an alternative drug may be preferable to the use of a laxative. By contrast, if pain control requires an opioid analgesic, it is rational to use a laxative to prevent drug-induced constipation.

Drugs unrelated to the diagnosis

The use of drugs that are not related to the diagnosis is irrational. A common example is the use of proton pump inhibitors (PPIs) which are often started on admission to hospital for chest pain of uncertain origin. When a diagnosis is made, such as myocardial ischaemia, the PPI is often continued.

Antibiotics

Inappropriate use of antibiotics for conditions unlikely to have a bacterial origin is irrational. Antibiotics are often included in the treatment of acute exacerbations of asthma, despite a normal temperature, normal white blood cell count and normal chest radiograph, when the trigger is more likely to have been a virus.

Expensive drugs

The use of unnecessarily expensive drugs when cheaper effective alternatives are available is often considered to be irrational prescribing. However, such drugs can frequently be justified if the alternatives are less effective or less well tolerated. When confronted with the choice of variably priced alternatives, there needs to be assessment of clinical trial evidence, the effect of habitual prescribing patterns and learned behaviour, and the potential influence of promotion by the pharmaceutical industry.

Dosage

Under-dosage with drugs can also be irrational. When evidence from clinical trials demonstrates benefit from a drug at a specified dose, this is often extrapolated in practice to smaller doses. For treatment of heart failure, the doses of an ACEI or beta-blocker that improve prognosis are well characterised. There is evidence that small doses are less effective, yet dose titration is often not followed up to the target doses used in the trials.

Involving the patient

The prescriber should try to understand the health beliefs and expectations of the patient regarding their treatment. Adherence to therapy is more likely if the patient understands the reason for taking a drug and is involved in the decision to prescribe. Patients are more likely to have confidence in the prescriber if given basic knowledge of potential adverse effects and advice on what to do if they occur. They should be made aware of how to take the drug and for how long they will need to take it.

Conflicts of interest

None.

Further reading

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