Evidence, risk and the patient

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Summary

Drugs are often assessed by their effect on surrogate outcomes, such as blood pressure or cholesterol, rather than clinical end points such as death. This results in risk factors being treated to prevent possible future events. Patients must be willing to take drugs for many years in the hope that they will obtain the same benefit as the patients in clinical trials. Patients in clinical trials are, however, often different from the patients seen in practice. It is therefore important to consider the whole patient and not just prescribe a drug to treat a risk factor in isolation. When deciding to prescribe, the absolute benefit of treatment should be discussed with the patient.

Key words: clinical trials.

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Introduction

Prescribing drugs to treat risk factors is a daily routine activity for most Australian general practitioners. Underpinning the pharmacotherapy of risk factors is evidence from clinical trials that is widely accepted to validate the merit of this treatment. However, many people may need to have their risk factors treated to prevent an adverse outcome for one person. Considering the whole patient is integral to the art of medicine, so we should consider the individual and not just their risk factors.

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[1] To apply this principle we have to assess what the evidence from clinical trials means.

Assessing evidence – the scientific dimension

The anatomical and pathophysiological mechanisms of disease, though important to understand, are not the evidence that underpins the validity of medical treatment. Medicine is essentially an observational science and clinical trials endeavour to determine significant differences between the natural history of disease and the effect of treatment. Some basic understanding of statistics is needed – especially when assessing risk factor modification.

Significance

A result is statistically significant when the 'p' value is less than 0.05. This arbitrarily chosen value means that there is a 95% likelihood that an observation is not due to chance. The p value is a measure of the reliability of an observation, but it does not quantify any effect.

The word 'significant' is frequently used inconsistently. A statistically significant result from a trial is sometimes erroneously interpreted as having a high clinical significance.

Reporting risk reductions

Trials look at the incidence of outcomes with and without intervention. Absolute risk reduction is the difference between the outcome in the control group and the outcome in the intervention group in a specified time period.

The relative risk reduction is the absolute risk reduction as a proportion of the baseline rate. A relative risk reduction often seems impressive, but it may only represent a small difference. For example, if the event rate is 0.2% in the control group and 0.1% in the intervention group the relative risk reduction is 50%, but the absolute risk reduction is only 0.1%.

One must always know whether a quoted risk change is relative or absolute. Benefits of treatment are often presented in relative terms, but harms and adverse effects are usually presented in absolute terms (Table 1).

Number needed to treat or harm

The number needed to treat is the number of patients who must be treated for a period of time to prevent one having

Table 1

Absolute and relative risk

Event rate control	Event rate intervention	Relative risk reduction	Absolute risk reduction	Number needed to treat	p value
20%	10%	50%	10%	10	< 0.05
4%	2%	50%	2%	50	< 0.05
0.2%	0.1%	50%	0.1%	1000	< 0.05

The p value measures the reliability of the observation, not the quantum of effect.
If the effect is small, a small p value can still be achieved with a large sample size.

the outcome of interest. It is the inverse of the absolute risk reduction (1/ARR). For example, if the absolute risk reduction after five years is 2%, then the number needed to treat is 50 (1/0.02). Fifty people need to be treated for five years to prevent one adverse outcome. This means that the outcome of interest will be unchanged for the 49 other people who took the treatment for five years. Some of these 49 people may come to harm as a result of adverse effects of treatment.

The number needed to harm is a less frequently published number. It is essentially the inverse of the absolute rate of adverse effects. Over 10 years, if 4% of women suffer venous thromboembolism while on hormone replacement therapy and 2% without hormone replacement therapy, the absolute harm rate of the therapy is 2% and the number needed to harm is 50. That is, for every 50 women treated one will develop a thrombosis that would not have otherwise occurred.[2]

Outcome

Trial end points are varied and one must have a clear understanding of the outcomes measured. Death, disability and morbidity are clinical end points, while others such as blood pressure, cholesterol or bone density are surrogate or intermediate markers. Surrogate end points may have merit as indicators of potential benefit, but they rely on other evidence providing a causal link to clinical outcomes. In the end all interventions must be justifiable by an improvement in patient well-being, that is, by clinical end points.

Assessing evidence – patient factors

Many trials exclude pregnant women, children, older people and patients with significant comorbidity. The benefit or harm in 'real world' patients may not be equivalent. Similarly, some treatments have only been studied in particular groups or after patients intolerant to test doses have been excluded (for example, the HOPE trial where 10% of the initial cohort were excluded after the run-in phase).[3]

Health professionals interact with individuals, not trial cohorts or populations. The characteristics of the individual patient are therefore an important consideration when deciding whether to treat a risk factor.

Patient attitude

Everyone has a different attitude to risk. The sedentary smoker who drinks a bottle of wine per day clearly has a different life attitude to a teetotal non-smoker who walks for an hour every day.

Patient anxiety

The label of 'risk' can cause some patients to become significantly anxious. The effect of labelling has been well documented to impair quality of life. This is particularly pertinent in the context of a symptomless risk factor and should be considered before introducing the issue of risk with patients.

Patient effort

Harm from treatment includes more than potential drug adverse effects. Treatment involves visits to the doctor, prescriptions, blood tests, possibly diagnostic imaging, cost and the daily consumption of drugs. When the benefit of treatment is a trust that the odds of some future event are reduced rather than an immediately experienced improvement in well-being, the effort to adhere to treatment can be significant.

Comorbidity

The outcome being prevented must be relevant to the patient. A critical phenomenon here is significant other disease. The quality of life gained is more important than the raw quantum. In patients with significant comorbidity, a physician needs to consider and discuss whether the benefit gained is worth the additional intervention. An example here is hypercholesterolaemia in a patient with advancing dementia. One may be able to reduce the risk of a cardiovascular event, but is this relevant to this patient?

Risky realities

The association of an observation with a negative outcome does not necessarily mean treating the observation improves the outcome. The transverse ear lobe crease has been associated with a higher risk of coronary artery disease.[4] Excision of the ear lobe is unlikely to change things. For many years it was stated that hormone replacement therapy reduced the risk of heart disease on the basis of plausible pathophysiological models. The Women's Health Initiative trial suggests the actual outcome was different.[2]

Risk is never zero and is never reduced to zero. At any age there is a risk of disease and even death. Drug therapy for cardiovascular risk reduces a baseline level of risk at best by a relative 50%. For example, in a person with known ischaemic heart disease whose absolute risk of another event may be 30% in five years, maximal risk factor reduction reduces that to 15% in five years. It is not reduced to zero, and in that time that individual still has various risks for injury or other illness. Prevention by drug therapy of risk factors is never absolute, contrary to prevention in other contexts such as immunisation, where a serious infectious disease prevented is one that will probably never occur.

There are quite distinct principles underlying treatment and prevention. All interventions have a risk of harm, but a person's willingness to accept the risk will depend on their situation. The rate of adverse reactions to chemotherapy may be acceptable to a cancer patient with a poor prognosis. However, a similar rate of adverse effects would not be acceptable for a vaccine given to many healthy individuals to prevent disease in a few. Similarly, the effort of treatment for symptomatic disease can be readily justified by the improvement in the symptoms, whereas

in risk factor modification the effort is now, for all, but the benefit is later, for some.

Who to treat?

Drugs are approved by the Therapeutic Goods Administration (TGA) if they are relatively safe and have reasonable evidence of efficacy. If the drug is cost-effective in a particular condition it will be listed on the Pharmaceutical Benefits Scheme (PBS). Similarly, treatment guidelines are expert interpretations of the evidence on how to achieve the best outcomes for a particular disease. However, the health professional's role is a step further beyond the TGA, PBS and guidelines to a focus on the outcome for the whole patient rather than just their disease. Specific consideration must be given to the individual relevance of the outcome being sought, and what information is suitable for a patient to make an informed decision.

Informing patients about risk

Patients should understand the benefits and harm of the treatment being offered, especially when this could be lifelong drug therapy. Relative risk reductions do not really quantify the merit of a treatment. Absolute data can be presented in several ways. Some authors recommend the Visual Rx analogue diagrams with a number of people represented as stick figures and the control and intervention groups marked in different colours or shades.[5] Other authors have shown that patients and physicians more readily understand outcomes by using natural frequencies[6] (such as, for 100 similar persons an event will occur in 10 without treatment and 7 with treatment) rather than percentages or odds ratios. Another technique is to ask the patient to imagine a room full of 100 similar people and compare the various outcomes for a number of those in that room.

Using natural frequencies and absolute risk data, a patient can be in a better position to assess the merit of a treatment in the context of their own attitudes, preferences, expectations and other morbidity. Absolute outcome data and number needed to treat have been published for many drugs.

Here are two examples of using absolute outcome data to assist with decision-making about preventive pharmacotherapy.

Sixty-year-old female with hypercholesterolaemia

The readily available New Zealand cardiovascular risk calculator[7] can quantify absolute risk. With a blood pressure of 130/80, total cholesterol of 7.5 mmol/L, and an HDL cholesterol of 1.1 mmol/L, a non-smoking non-diabetic female has a five-year cardiovascular event risk of 7%. It is generally agreed that statins will reduce risk by a third. With treatment the five-year risk is thus about 5%.

When discussing the merit of treatment against the effort and potential adverse effects, consider the absolute risk reduction. About seven in 100 people will have an event in five years with no treatment, but if 100 take the statin for five years, five will have an event.

Overweight patient taking metformin for type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS)[8] showed a difference in diabetic end points over 10 years between 'conventional' treatment (fasting glucose < 15 mmol/L, and no hyperglycaemic symptoms) and 'intensive' treatment (glucose < 6 mmol/L). With conventional treatment macrovascular complications occurred in 31% of patients and microvascular in 9.2%. With intensive treatment including metformin, the rates were 23% and 6.7%.[3] The prescriber and patient should discuss the downside of intensive treatment with respect to hypoglycaemia, metformin adverse effects such as diarrhoea, and the patient effort required to achieve a fasting glucose < 6 mmol/L.

Conclusion

Risk factor pharmacotherapy is underpinned by population-based research. In contrast, the primary care physician has to decide what to recommend or do with each individual patient. An understanding of the limitations of epidemiological evidence, a familiarity with using absolute outcome data, an acknowledgement of the ethical perspectives and a focus on the whole patient should ensure that pharmacotherapy for risk factors is useful and relevant to the patient.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 55)

7. A reduction of greater than 50% in relative risk confirms a clinically significant intervention.
8. Treating risk factors reduces adverse outcomes but cannot prevent them completely.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Dasatinib

Sprycel (Bristol-Myers Squibb)

20 mg, 50 mg and 70 mg tablets

Approved indication: chronic myeloid leukaemia and acute lymphoblastic leukaemia

Australian Medicines Handbook section 14.3.5

Most patients with chronic myeloid leukaemia have a chromosomal translocation that produces the Philadelphia chromosome (Ph). This results in an abnormal tyrosine kinase which causes cells to become malignant. This translocation can also occur in patients with acute lymphoblastic leukaemia.

Imatinib (see New drugs, Aust Prescr 2001;24:129–31) is an inhibitor of this abnormal tyrosine kinase and is effective in many patients with newly diagnosed chronic myeloid leukaemia. However, some patients are resistant to imatinib when they start therapy or develop resistance during therapy due to mutations in the abnormal tyrosine kinase gene. These mutations interfere with imatinib binding.

Dasatinib is a new tyrosine kinase inhibitor that binds to a broader range of kinases compared to imatinib. *In vitro*, dasatinib has been shown to have inhibitory activity against imatinib-resistant leukaemia cell lines.

After oral administration of dasatinib, maximum plasma concentrations are observed within 0.5–3 hours and it has an overall mean terminal half-life of 5–6 hours. Dasatinib is extensively metabolised, mainly by cytochrome P450 3A4, and is predominantly eliminated in the faeces as metabolites.

Other drugs that inhibit cytochrome P450 3A4, such as erythromycin and other macrolides, may increase exposure to dasatinib and should be avoided. Likewise, inducers of cytochrome P450 3A4, such as dexamethasone, rifampicin, carbamazepine and St John's wort may reduce the concentrations of dasatinib and are not recommended. Dasatinib increases the risk of toxicity from other cytochrome P450 3A4 substrates that have a narrow therapeutic index, such as quinidine and ergot alkaloids. H_2 blockers and proton pump inhibitors are likely to reduce the oral bioavailability of dasatinib and are not recommended. If antacids are used, they should be given two hours before or after taking dasatinib.

The efficacy of dasatinib was first assessed in a phase I dose-escalation study in 84 patients with chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia who could not tolerate or were resistant to imatinib. Patients received 15–240 mg of dasatinib orally per day. Following treatment, 68 (81%) patients had a major haematological response (assessed by counting white blood cells, platelets, blasts and myelocytes and metamyelocytes in peripheral blood), and 37 (44%) patients had a major cytogenetic response (based on the percentage of Ph-positive cells in metaphase in bone marrow). Responses were maintained in 95% of patients with chronic-phase disease (median follow-up of 12 months) and 82% of patients with accelerated disease (median follow-up of 5 months). Most patients with lymphoid blast crisis or Ph-positive acute lymphoblastic leukaemia relapsed within six months.[1]

An open-label phase II trial studied the efficacy of dasatinib (70 mg taken twice a day) in 186 patients with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukaemia. After eight months, 168 (90%) patients achieved complete haematologic responses and 97 (52%) achieved major cytogenetic responses. Sixteen patients developed progressive disease or died.[2]

Another study assessed the efficacy of dasatinib (70 mg taken twice a day) from combined data of open-label phase II trials in patients (resistant or intolerant to imatinib) with chronic myeloid leukaemia in blast crisis. Of these patients, 74 had myeloid blast crisis and 42 had lymphoid blast crisis. After 8 months,