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Evaluation of treatment risks: taking clinical data, pharmacology and patient characteristics into account

● **The risks of a given treatment to an individual patient are assessed on the basis of evidence from evaluations of the treatment, pharmacological arguments and consideration of certain patient-specific characteristics.**

● **Knowledge of the adverse effects of a treatment, based on data from trials, studies and pharmacovigilance, contributes to the evaluation of the risks to which patients are exposed.**

● **Clinical trials are not the ideal way to study adverse effects. It is better to gather other types of information (including pharmacological and physiological data) to generate a sufficiently solid body of evidence with which to "manage uncertainty".**

● **Patient characteristics must be taken into account to determine whether they constitute risk factors for the adverse effects of treatment.**

● **Patients should be informed about the potential risks as well as the anticipated benefits of a treatment, so that they have the means to actively participate in assessing the risk-benefit balance of their own treatment.**

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Are there any risks associated with the treatment being offered? Are these risks common? Are they serious? Will the treatment that is recommended compromise the effectiveness of other medications I am taking?

Answering these basic questions, expressed explicitly or implicitly by patients, is part of the health professional's duties.

How should treatment risks be assessed? Answers can be found in evaluations of the treatment, such as reviews published in *Prescrire*, but also by erring on the side of caution and carefully considering the specific characteristics of the individual patient.

This article is not based on the usual *Prescrire* literature search, but rather on the *Prescrire* editorial staff's thoughts on the evaluation of treatment risks, as well as a few important *Prescrire* references. The sole aim of this article is to help readers to develop their own approach to the assessment of treatment risk within a broader framework that balances potential benefits against potential harmful effects (**a**). Its scope is not limited to drug treatments.

Gathering data on the adverse effects of a treatment and managing uncertainty

Knowledge of the adverse effects of a treatment plays a major role in the evaluation of the risks to which patients are exposed.

Such knowledge is only partly based on clinical trial data. Other sources of information are often more useful.

Clinical trials are not the ideal way to study adverse effects. Clinical trials usually demonstrate the frequent adverse effects of treatments. The rare, but potentially severe, adverse effects are rarely identified during trials (1).

However, analysing the mild but common adverse effects reported in clinical trials can predict the possibility of a "pyramid", with a large number of mild adverse effects at the base and a small number of serious adverse effects at the apex. For example, mild skin disorders observed during clinical trials raise the possibility that serious adverse cutaneous reactions such as Lyell's syndrome might occur. As another example, elevation of transaminases raises the possibility that a few cases of fulminant hepatic necrosis might occur.

Clinical analysis of serious events occurring in a small number of patients during clinical trials suggests that the number of cases may become problematic when the treatment is applied on a broader scale, in the general population.

Moreover, the patients enrolled in clinical trials are selected and are not representative of patients encountered in routine clinical practice. Patients with renal impairment or comorbidities, the elderly, or pregnant women are rarely included in clinical trials. Therefore, no data are available on adverse effects in these at-risk patients.

Nevertheless, the breast cancer risk associated with postmenopausal hormone replacement therapy and the cardiovascular risks of cox-2 inhibitors were demonstrated in clinical trials (2,3). Clinical trial data must be examined carefully however: the cardiovascular risks of cox-2 inhibitors were long overlooked although the data were convincing (4). The self-harm and aggressive behaviour associated with "selective" serotonin reuptake inhibitor antidepressants went unnoticed for a long time, particularly due to the vocabulary used to classify the adverse effects. For example, the episodes of violence or aggression were described as "hostility", without taking their severity into account (5).

A few troubling reports often suffice as a warning. Observational studies are subject to many types of bias. But they have informative value because they arouse safety concerns when a signal is detected (**b**).

Reports from health professionals or patients, in the form of detailed case reports or spontaneous reporting to pharmacovigilance organisations around the world, carry considerable weight. The vast majority of new adverse effects that come to light once a drug is on the market are discovered through spontaneous reporting by health professionals, and increasingly by the patients themselves.

A few high-quality reports from a few clinicians were sufficient to identify the extrapyramidal adverse effects of *trimetazidine*; osteonecrosis of the jaw or atypical fractures associated with bisphosphonates; skin ulceration associated with *nicorandil*; and limb atrophy associated with in utero exposure to *thalidomide* (6-10).

Pulmonary hypertension caused by amphetamine-like anorectics was identified through cases reported by health professionals. The only "advantage" provided by the epidemiological studies conducted to confirm this risk was to delay the decision to withdraw these drugs from the market.

Managing uncertainty by basing decisions on a body of evidence. On the whole, adverse effects of treatments are not studied as thoroughly as their benefits. A great deal of uncertainty exists and there is insufficient data about the adverse effects of treatments, particularly about the most recent ones (minimising risk also involves using older drugs, about which more is known). As adverse effects are often discovered through individual case reports or case series, the level of evidence is considered low. However, this body of evidence is often sufficient when the aim is to avoid causing harm.

For drug treatments, also take pharmacology and physiology into account

In order to evaluate the risks of a drug, particularly a recent drug, it is useful to consider the known adverse effects of other drugs in the same pharmacotherapeutic group or those that are chemically related. Thus, *tianeptine* dependence and addiction could have been predicted because of its similarity to *amineptine*, which is known to expose patients to these adverse effects (11). Pulmonary hypertension and valvular heart disease associated with *benfluorex* could have been predicted because of its similarity to *fenfluramine* (12). [see also on page 17]

Knowing the pharmacodynamic effects of a drug makes it possible to deduce a series of adverse effects that share the same mechanism: for example, atropine-like or amphetamine-like effects or serotonergic effects. Adverse effects of cox-2 inhibitors were predictable, based on the adverse effects of anti-inflammatory drugs and cyclooxygenases (3). Abuse and dependence associated with *zopiclone* and *zolpidem* could have been predicted from their pharmacological effects, which are similar to those of the benzodiazepines (13).

Certain mechanisms, such as hypersensitivity, increase the likelihood of adverse reactions, such as rapid progression or the possibility of multiple organ damage.

Knowing how drugs are metabolised. When assessing a drug's risks, a few aspects of its metabolism should be considered: specifically, whether it is excreted by the kidneys, whether it is metabolised by saturable enzyme systems, whether its transport mechanisms are subject to competition or whether its gastrointestinal absorption might be subject to interference.

These types of data can be used to predict drug accumulation in patients with renal or hepatic impairment, or pharmacokinetic drug interactions, for example.

Knowing that low molecular weight heparins are excreted by the kidneys, bleeding in the elderly or in patients with renal impairment could have been anticipated.

The adverse effect profile: a fundamental tool. Adverse effect profiles are based on a body of evidence, taking into account the level of evidence of each finding and data consistency. This profile corresponds to a list of a drug's adverse effects classified according to their frequency and severity.

The adverse effect profile of a drug provides an overview of all its known adverse effects in an easily remembered and classified format. It is a fundamental tool for evaluating the risks to which patients are exposed. The *Prescrire* guide for preventing the adverse reactions resulting from drug interactions (in French) is based on these principles.

Taking patient characteristics into account: essential

The information available to health professionals for assessing treatment risks is mainly based on scattered data from large groups of patients, expressed as "average" values.

When deciding how to treat an individual patient, that patient's specific characteristics must be taken into account as much as possible. The patient probably differs from the "average" patient enrolled in studies or trials in some respects.

Which characteristics presented by an individual patient constitute risk factors for a particular adverse effect?

Does the patient have pre-existing cardiac disorders that predispose him or her to certain adverse effects of a specific drug? Is there any impairment of organs involved in drug elimination (kidney or liver failure in particular) that puts the patient at greater risk of drug accumulation and dose-dependent adverse effects (particularly the case in elderly patients)? Is the patient currently taking any medications that might cause pharmacodynamic interactions due to additive adverse effects? Does the patient have any physical or psychological characteristics making him or her susceptible to the adverse effects of a particular surgical procedure or psychotherapy intervention?

In conclusion

Evaluation of a treatment's risks, as well as its benefits, plays an essential role in choosing the most appropriate treatment strategy. When drugs are first marketed, information about their adverse effects is limited. This body of data grows slowly as more clinical experience is obtained with the drug.

Informing patients about the potential risks, as well as the expected benefits, of a treatment gives them the means to take an active role in assessing the risk-benefit balance of their own treatment. It gives them the means to participate in making an informed decision about the most appropriate therapy.

a- Based on the concepts of the evaluation of treatment benefits, see ref. 14.

b- A signal, in this case, refers to an event or transgression of a pre-defined threshold, which should receive particular attention during surveillance.

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "Effets indésirables mal rapportés dans les essais" *Rev Prescrire* 2001; **21** (218): 439.
2- Prescrire Rédaction "Traitement hormonal substitutif de la ménopause et cancer: attention au sein" *Rev Prescrire* 2003; **23** (235): 28.
3- Prescrire Editorial Staff "Cox-2 inhibitors: cardiovascular adverse effects" *Prescrire Int* 2002; **22** (231): 596-597.
4- Prescrire Rédaction "Réagir à la mainmise des firmes sur les données cliniques" *Rev Prescrire* 2009; **29** (303): 57.
5- Prescrire Rédaction "Antidépresseurs IRS et violence" *Rev Prescrire* 2008; **28** (296): 431-432.
6- Prescrire Editorial Staff "Reversible Parkinsonism linked to trimetazidine" *Prescrire Int* 2005; **14** (76): 63.
7- Prescrire Rédaction "Ostéonécroses de la mâchoire sous disphosphonate" *Rev Prescrire* 2004; **24** (256): 833.
8- Prescrire Editorial Staff "Bisphosphonates: atypical fractures?" *Prescrire Int* 2009; **18** (99): 25.
9- Prescrire Rédaction "Nicorandil: ulcérations cornéennes aussi?" *Rev Prescrire* 2008; **28** (301): 835.
10- Prescrire Rédaction "Le thalidomide, trente ans après" *Rev Prescrire* 1991; **11** (108): 303-304.
11- Prescrire Rédaction "Toxicomanie à la tianeptine" *Rev Prescrire* 2000; **20** (211): 756.
12- Prescrire Editorial Staff "Hidden amphetamines: from smoking cessation to diabetes" *Prescrire Int* 2003; **12** (69): 18-20.
13- Prescrire Editorial Staff "Zolpidem and zopiclone: hypnotic dependence" *Prescrire Int* 2001; **10** (51): 15.
14- Prescrire Rédaction "Évaluer les bénéfices d'un traitement: d'abord les critères cliniques utiles aux patients" *Rev Prescrire* 2008; **28** (291): 69-70.