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Preventability of Drug-Related Harms – Part II

Proposed Criteria, Based on Frameworks that Classify Adverse Drug Reactions

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Abstract

Background: 'Preventability' is a crucial concept in the literature on adverse drug effects. However, a systematic review of the definitions of preventability of adverse drug effects has suggested that none fits all circumstances. Furthermore, when the reliability of these definitions has been examined they have been found to be imperfect.

Objective: To propose and outline a method for determining the theoretical preventability of an adverse drug effect, based on frameworks for classifying adverse drug reactions – the EIDOS and DoTS methods.

Methods: EIDOS is based on the mechanism of action of the drug. It observes that a drug (an **E**xtrinsic species) causes an adverse effect by interacting with an **I**ntrinsic species that is its target when the two are **D**istributed together, and that the resulting pathophysiological **O**utcome (the adverse effect) causes the **S**equela (the adverse reaction).

DoTS observes that the **Do**se-relatedness of the adverse effect compared with the beneficial effect is relevant (determining toxic, collateral, or hypersusceptibility effects), that adverse effects have **T**ime-courses (varying from immediate to delayed), and that there are individual **S**usceptibility factors.

Results and Discussion: We have elicited many published examples that show that each of these factors in the causation of an adverse drug effect can be adduced to assess its preventability. We have constructed a flowchart that illustrates how the processes can be logically analysed.

Conclusions: This approach suggests methods for devising prospective preventive strategies and for deciding retrospectively whether an adverse reaction in an individual should have been prevented.

Background

Preventability (sometimes referred to as 'avoidability') is a crucial concept in the literature on adverse events, including suspected adverse drug reactions and other drug-related harms (sometimes called 'drug-related morbidity', 'drug-related problems', or 'adverse drug events').

There are two aspects to preventability: whether in principle an event is preventable in the absence of error (the general problem, which can be considered prospectively or retrospectively); and, if it is, whether we can in fact prevent it (the individual problem, usually considered retrospectively after harm has arisen). For example, penicillin hypersensitivity reactions can in principle be avoided in patients known to be susceptible, by not giving the drug; however, in practice such reactions will occur, for example because information is not available to the prescriber or because the predictive test available (skin prick testing) is not entirely reliable.

There have been many attempts to devise ways of judging whether an adverse effect of a drug is or is not preventable. Others have pointed out that the methods that have been used for judging preventability of adverse drug effects have not been properly evaluated.[1] We have carried out a systematic review of all published methods, and we believe that our analysis (see Part I, this issue of *Drug Safety*),[2] in which we have discussed their limitations, demonstrates the imperfections of those methods.

Here we outline a novel method for judging preventability, based on frameworks that classify adverse drug reactions. Although we shall discuss the general principles of preventability rather than practical prevention, we shall include illustrative examples of preventive measures based on these preventability criteria.

In doing this we are aware that although harms may be theoretically preventable, in practice they are never *absolutely* preventable. However, any intervention that reduces the probability of harm can be said to have made a contribution to prevention.

Methods

A Systematic Review of Previous Methods for Judging the Preventability of an Adverse Drug Reaction

We have described our systematic review in Part I.[2] In this we identified eight different general approaches that have previously been used to define the preventability of adverse drug reactions: (1) analysis without explicit criteria; (2) expert consensus; (3) preventability linked to error; (4) preventability linked to standards of care; (5) preventability linked to medication-related factors; (6) preventability linked to information technology; (7) categorization of harmful treatments in explicit lists; and (8) a combination of more than one approach. These approaches rely on two general methods: the judgement of one or more investigators or the use of pre-defined explicit criteria. Our analysis in the accompanying review suggests that neither method is satisfactory.

A New Method for Determining the Theoretical Preventability of an Adverse Drug Reaction

We think it is helpful to consider preventability mechanistically, according to the nature of the adverse reaction, rather than the way in which it arises or the context in which it occurs. We are concerned here with analysing the preventability of associated drug-adverse event pairs, whatever the source of the harm (i.e. whether error can be detected or not). We are not primarily concerned with whether prevention is possible in practice, although we shall give examples of relevant preventive strategies to show how the method works.

The method involves classifying adverse drug reactions by mechanism and by clinical manifestations to inform judgements about theoretical preventability. We have used the EIDOS system to classify mechanisms and DoTS to classify the clinical manifestations (figure 1). DoTS is based on (i) the Dose-relatedness of the adverse effect compared with the beneficial effect; (ii) the Time-course of the reaction; and (iii) the Susceptibility characteristics of the patient in whom the drug is used, although it is logical to consider these factors in the reverse order. In the following section we describe the EIDOS and DoTS frameworks.

EIDOS and DoTS: Frameworks for Classifying Adverse Drug Reactions

The EIDOS and DoTS frameworks describe firstly what happens when a drug interacts with tissues in the body, causing a pathophysiological

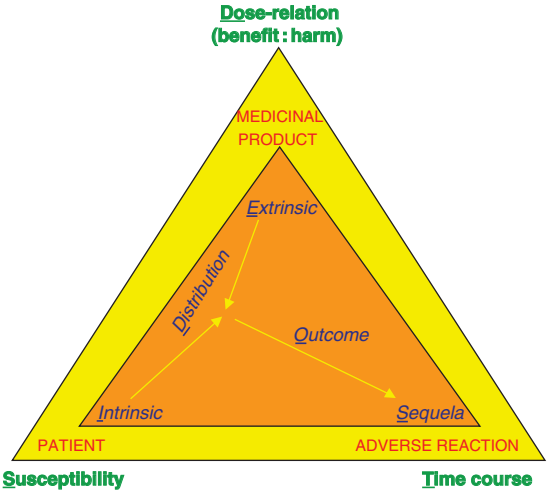

Fig. 1. Classifying adverse drug reactions. An adverse reaction occurs when a drug is administered to a patient (red upper case text). Adverse reactions can be classified mechanistically (EIDOS; blue italicized text) by noting that the Extrinsic (drug) species, when co-Distributed with an Intrinsic (patient) species, has a pharmacological or other effect (the Outcome), producing the adverse effect (the Sequela). It can be further classified (DoTS; green bold text) by considering the three main features of the adverse reaction – its Dose-relatedness, its Time-course, and individual Susceptibility (reproduced from Ferner and Aronson,[3] with permission from Adis, a Wolters Kluwer business [© Adis Data Information BV 2010. All rights reserved]).

outcome that results in an adverse effect (EIDOS) and, secondly, the clinical features of that effect, i.e. the adverse reaction (DoTS). These frameworks are inter-related, as shown in figure 1. They both spring from the observation that an adverse reaction occurs when a drug is administered to a patient and causes an adverse effect. EIDOS describes the drug–patient–effect triad as it happens and DoTS describes the main features of each member of the triad that is involved in the reaction. The schema that links these two frameworks (figure 1) is not a theoretical construct. It is a description of what actually happens, based on what is knowable (EIDOS) and observable (DoTS). Of course, we do not always have enough knowledge to describe EIDOS fully nor enough observations to describe DoTS fully, but that does not vitiate the frameworks or the schema that links them.

Results and Discussion

Preventability According to the Mechanism of the Reaction

The EIDOS framework describes how an adverse drug effect arises mechanistically. It observes that an Extrinsic chemical species[1] (E) initiates the effect; that it interacts with an Intrinsic chemical species (I); that for the interaction to occur the two species must be co-Distributed (D) in the body; and that this interaction produces a (physiological or pathological) Outcome (O) [the adverse effect], which leads to the Sequela (S), i.e. the adverse drug reaction.[3] Each of these may be relevant in assessing the preventability of an adverse reaction, especially when the mechanism is well understood.[4]

Knowledge of the *extrinsic chemical species* can help to prevent adverse reactions in several ways, for example by predicting allergic cross-reactivity, eliminating excipients, adulterants, and contaminants, identifying safer metabolites of a drug that causes an adverse effect, or avoiding the formation of a compound that causes an adverse reaction (e.g. by chemical deterioration during storage).

When the *intrinsic* species is known – for example, the relevant receptor subtypes for therapeutic and adverse effects – steps can be taken to mitigate the latter pharmacodynamically, for instance by using receptor antagonists or by physiological or physicochemical counteraction.

The *distribution* of the relevant extrinsic and intrinsic species can inform preventability pharmacokinetically, either by avoiding exposure of the site of the potential adverse effect or by preventing or mitigating the adverse effect where it occurs.

Examples are shown in table I.

Preventability According to Individual Susceptibility Factors

Knowledge of susceptibility factors allows avoidance in those who are susceptible. For examples see table II.

Some susceptibility factors determine absolutely whether a patient will develop an adverse reaction; for example, a susceptibility to type I hypersensi-

1 A chemical species is "a particular kind of molecule, ion, free radical, etc." (Oxford English Dictionary).

Table I. Preventability of adverse drug reactions according to mechanism

Mechanistic factor	Potential preventive strategy related to mechanism	Examples
Extrinsic species	(a) Knowledge of cross-reactivity	(a) Beta-lactam antibacterials[5]
	(b) Elimination of excipients, adulterants, or contaminants	(b) Eosinophilia-myalgia syndrome (tryptophan)[6]
	(c) Replacing the parent compound with an active metabolite	(c) Fexofenadine replacing terfenadine[7]
	(d) Defining storage conditions (e.g. limiting shelf-life)	(d) Tetracycline-induced Fanconi syndrome[8]
Intrinsic species	Potentially preventable at the level of the target of the adverse effect (e.g. the receptor) (a) Direct interaction at the site of the adverse effect (b) Physiological counteraction	(a) Atropinic drugs to block the muscarinic actions of acetylcholinesterase inhibitors (e.g. neostigmine) while preserving their nicotinic actions in treating myasthenia gravis[9]
		(b) Atropinic drugs to relieve Parkinsonism due to dopamine receptor antagonists
Distribution	(a) Administration at a distance from the site of the adverse effect	(a) Eye drops, inhaled drugs
	(b) Reducing the access of the drug to the site of the adverse effect (c) Prevention at the site of the adverse effect	(b) Levodopa + a dopa decarboxylase inhibitor; H_1 receptor antagonists (antihistamines) with poor brain penetration
		(c) Haemorrhagic cystitis due to cyclophosphamide and ifosphamide prevented by mesna[10]

tivity reactions from penicillins. However, most susceptibility factors merely increase the probability that the adverse effect will occur; for example, while Afro-Caribbean patients are five times more likely than others to develop angio-oedema with ACE inhibitors, the absolute risk is still small.[15]

Known history of susceptibility: When a patient is known to be hypersusceptible to a drug, adverse effects can be prevented by not using it. Conversely, if a patient is known not to be susceptible, the question of preventability does not arise.

Tests of susceptibility: If a test of suitable sensitivity and specificity is available it can be used to determine whether the patient is of sufficient susceptibility for the drug to be avoided.

Preventability According to the Time-Course of the Reaction

Each adverse drug reaction has a characteristic time-course, which can influence preventability. For examples see table III.

Table II. Preventability of adverse drug reactions according to individual susceptibility

Knowledge of susceptibility	Test of susceptibility, with good sensitivity and specificity	Preventability by considering susceptibility	Examples
Known history of susceptibility	Not required	Preventable	Penicillin hypersensitivity G6PD deficiency
Not known whether susceptible	Available and practicable	Preventable	*In vitro* caffeine-halothane muscle contracture test (malignant hyperpyrexia)[11] Thiopurine methyltransferase phenotyping (azathioprine or mercaptopurine)[12] HLA B*5701 genotyping (abacavir hypersensitivity)[13]
	Available but not practicable	Not practically preventable[a]	SLCO1B1 genotype (statin-induced rhabdomyolysis)[14]
	Not available	Not preventable[a]	
Known not to be susceptible	Irrelevant		

a In some such cases a test dose may be helpful.

G6PD = glucose-6-phosphate dehydrogenase; **SLCO** = solute carrier organic anion transporter.

Table III. Preventability of adverse drug reactions according to time-course

Time-course	Potential preventive strategy related to time	Examples
Time-independent	See toxic reactions (table IV)	
Immediate	Infuse the drug slowly	Vancomycin (red-man syndrome)[16]
First dose	Specific preventive measures known for some adverse reactions	ACE inhibitors in congestive heart failure – give a low first-dose while the patient is lying down
Early tolerant	Slowly increase the dose	Carbamazepine and dizziness[17]
Early persistent	Generally not preventable	Early adverse effects of corticosteroids
Intermediate	Can sometimes be mitigated by monitoring	Clozapine and neutropenia
Late	Limit duration of therapy	Short courses of corticosteroids
Late – due to withdrawal	Slow withdrawal	Propranolol in patients with angina (risk of myocardial infarction)[18]
Delayed	Limit duration of therapy Prevention during the susceptible period	Ciclosporin (skin cancers) Isotretinoin (contraception to avoid teratogenicity)[19]

Immediate reactions occur only when the drug is administered rapidly intravenously (e.g. vancomycin and the red-man syndrome); prevention is by infusing the drug slowly.

Reactions that occur after the *first dose* of a course can sometimes be prevented by precautionary measures, such as using a low first dose when giving ACE inhibitors in congestive heart failure.

Early reactions associated with tolerance, such as dizziness due to treatment with carbamazepine, can be mitigated by slow titration of the dose. Early reactions that persist generally cannot be prevented by a strategy that involves their time-course.

Intermediate reactions, such as neutropenia due to treatment with clozapine, can be mitigated if it is possible to monitor for the reaction during the period when it is most likely to occur.

Late reactions, such as iatrogenic Cushing's syndrome from corticosteroids, occur after prolonged treatment; using short courses of treatment can prevent these. *Late* reactions due to drug withdrawal, such as rebound hypertension after treatment with clonidine, can be prevented or mitigated by slow withdrawal.

Delayed reactions include teratogenicity, which can be prevented by using contraception or by avoiding administration of the causative drug

Table IV. Preventability of adverse drug reactions according to the dose-response pattern

Dose-response pattern	Preventive strategy related to dose	Examples
Toxic	(a) Limit the dose to prevent adverse effects; monitor if possible	(a) Gentamicin (plasma concentration monitoring) Insulin (blood glucose monitoring)
	(b) Use divided doses or a modified-release formulation to avoid peak plasma concentrations	(b) Carbamazepine nervous system effects[24]
Collateral	(a) Not preventable by manipulating the dose, without also losing the beneficial effect	(a) Anticholinergic effects of tricyclic antidepressants
	(b) Use of low-dose combinations	(b) Hypertension treated with low-dose combinations of different antihypertensive classes of drugs[25]
	(c) Mechanistic prevention when the adverse and beneficial effects have different mechanisms	(c) Atropine to prevent the muscarinic effects of neostigmine, whose nicotinic effect reverses neuromuscular blockade
Hypersusceptibility	(a) Not preventable by manipulating the dose	(a) Penicillin allergy
	(b) Desensitization	(b) Clopidogrel[26]
	(c) Sometimes predictable by using a very low test dose	(c) Amphotericin anaphylaxis[27]

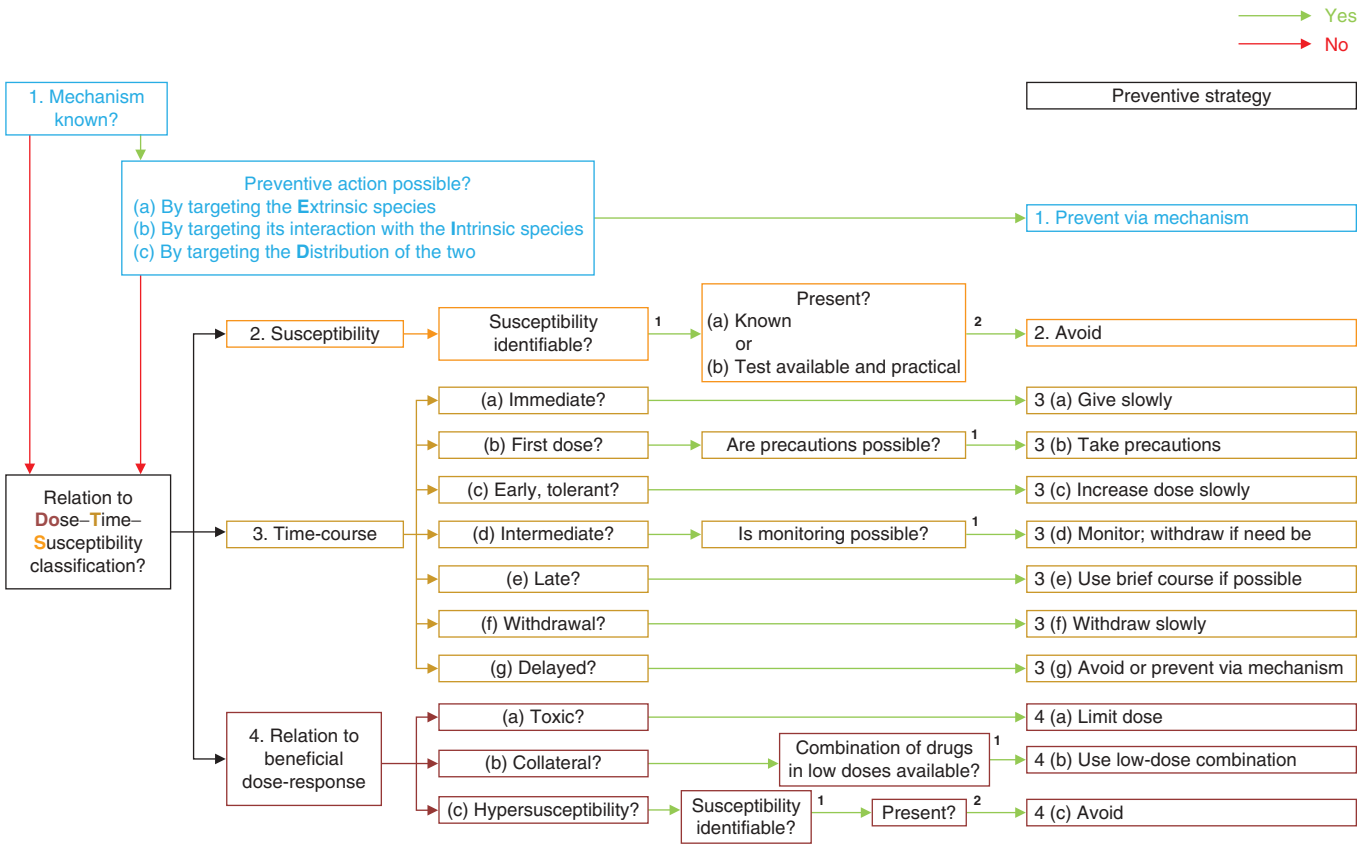

Fig. 2. A flowchart showing how preventive strategies can be determined by considering the pharmacokinetic and pharmacodynamic mechanisms of the adverse effect (EIDOS framework) and the susceptibility of the patient, the time-course of the reaction, and the dose-responsiveness of the reaction (DoTS framework). **1** If the answer is 'no' the effect is not preventable by this means. **2** If the answer is 'no' there is no increased risk.

to women who are, or may become, pregnant; and carcinogenicity, which can be prevented by limiting overall exposure to the drug, as in the case of smoking and lung cancer.[20]

Preventability According to the Dose-Relatedness of the Reaction

The Type A/B classification of adverse drug reactions assumes that 'dose-related' reactions are preventable and 'non-dose-related' reactions are not.[21] However, as we have shown elsewhere, this is an inaccurate and incomplete view of the dose-responsiveness of adverse reactions.[22] We have described three possible relations between the dose-responsiveness of beneficial and adverse drug effects – toxic, collateral, and hypersusceptibility effects.[23] For a summary, with examples, see table IV.

Toxic adverse effects occur either through an excess of the desired action (for example, hypoglycaemia due to treatment with insulin) or via a different mechanism whose dose-response curve lies to the right of the therapeutic dose-response curve (for example, penicillin-induced seizures). In such cases, the effect can be prevented by limiting the drug dosage or concentration.

Collateral adverse effects occur when the dose-response curves for benefit and harm are close together and are either mediated by different mechanisms or mediated by the same mechanism in different tissues. In such cases the two effects cannot be separated and adverse reactions are not preventable by altering the dose. For example, the anticholinergic effects of tricyclic antidepressants occur at the same concentrations as their antidepressant effects; any diminution in one by dosage reduction will be accompanied by a corresponding diminution in the other. However, collateral adverse effects can sometimes be prevented by using low doses of drugs with similar beneficial effects and different adverse effects; the beneficial effects sum and the adverse effects are minimized. Another method of preventing a collateral adverse effect is by attacking its mechanism, if known, without altering the beneficial effect, when the latter has a different mechanism.

Hypersusceptibility effects cannot be prevented when there is no known history and no established predictive marker. In some cases, desensitization may be possible. In other cases it may be possible to predict an adverse effect, such as anaphylaxis from amphotericin, by giving a low test dose, and then to prevent it by avoiding the drug.

A Flow Chart for Analysing Preventability of Adverse Drug Reactions

All of these concepts are combined in the flow chart shown in figure 2. This provides a logical framework for analysing adverse drug reactions in terms of their preventability and showing the preventive strategies that can be used.

Conclusions

This analysis shows that there is no simple method for determining the theoretical preventability of an adverse drug reaction. A complete analysis requires consideration of the pharmacokinetic and pharmacodynamic mechanisms of the reaction, its dose-responsiveness, its time-course, and individual susceptibility factors. Furthermore, each characteristic of a drug dictates a different preventive strategy; conversely, a particular strategy need not apply to all drugs of similar characteristics. This implies that previous estimates of the extent to which adverse reactions are preventable in a population are likely to be misleading.

The approach that we describe can be used to decide retrospectively whether an adverse reaction in an individual patient might have been preventable, and we have provided many examples. We have also devised a flow chart of general preventive strategies that could be used prospectively to reduce drug-related harm (figure 2). An analysis of a wide range of adverse drug reactions, classifying them using these systems, would show how many reactions are of the different types, and would identify reactions that ought to be preventable.

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