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Clarification of Terminology in Drug Safety

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Abstract

Nomenclature surrounding drug safety needs to be clear and unambiguous, so that patients, prescribers, manufacturers, and regulators can all understand each other. In particular, it needs to make it clear how adverse events and drug therapy are related to one another, how they are best classified, and their frequency, intensity and seriousness.

In this article, we therefore discuss and define terms used in the field of drug safety, particularly terms that are sometimes misunderstood or misused, including medicinal product, pharmaceutical formulation, excipient, adverse event (or experience) and adverse drug reaction (or effect). We also discuss terms used to define the seriousness, intensity, and risk of adverse reactions, and their classification.

Instead of creating definitions from scratch, as is commonly done, we have taken the novel approach of critically examining definitions that have been proposed or widely used and have formulated new or modified definitions based on a logical appraisal of their merits and demerits. We hope that these definitions will lead to discussion that will allow a corpus of satisfactory definitions to be widely agreed.

"*There is a large variety of names in medical publications for the untoward symptoms that follow the use of drugs…in England they are sometimes called* '*unpleasant symptoms*'" – translated from Louis Lewin, Die Nebenwirkungen der Arzneimittel (1881)

Consistent terminology is essential to good communication. This is especially true in the field of drug safety, because although the surveillance and reporting of adverse drug reactions cross international boundaries, the common language is English, the use of which is fraught with difficulty, even for native speakers.

In this article we discuss terms that are used in the field of drug safety, particularly terms that are sometimes misunderstood or misused, in the hope that a proper understanding of the genesis and the standardised use of these terms will improve communications in the field.

We have taken a novel approach to the problem of definition, by commenting on competing definitions. Where there is a satisfactory definition, we have argued for its adoption. When there is not, we have discussed the problems and have logically identified the reasons for the definitions that we have proposed, using published examples from clinical practice. For example, take the term 'adverse drug event', a term that has gained some popularity. We show that the term is problematic and illustrate the problem with a Venn diagram.

Some have argued that primary consensus is necessary to achieve good definition. We disagree. Many of the definitions that have been proposed in this field have been fabricated by committees and many of them are unsatisfactory. When they have

been published they have been handed down as *ex cathedra* statements, without any indication of the thought processes that have gone into producing them. As others have pointed out, because disagreement on such committees is rife, consensus in healthcare is reached only on "bland generalities that represent the lowest common denominator of debate and are embalmed as truths".[1] Nevertheless, we invite comments about our proposed definitions and we hope that ensuing discussions will result in the acceptance of definitions that have been through a rigorous process of formulation.

The importance of good definitions is illustrated by the difficulties that clinical academics are likely to face under the constraints of the new directive from the European Commission (2001/20/EC), known as the Clinical Trials Directive. In this document the definitions of terms such as 'clinical trial', 'non-interventional trial', and 'investigational medicinal product' have been constructed in order to meet specific regulatory desiderata, rather than in an attempt to be clear about what these things really are. The problems that these definitions will cause have not yet been fully explored.[2]

1. Terms that Describe Medicines and Formulations

1.1 Medicinal Product

The term 'medicinal product' was defined in an EU directive (2001/83/EC) as: (i) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (ii) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

The meaning of 'substance' here is further defined as including any matter, irrespective of origin – human, animal, vegetable, or chemical. Other definitions, such as those used in Australia and New Zealand, are similar and often refer to the EU definition. However, the EU definition omits some important uses of medicinal products, including their use as placebos.

Confusingly, the term 'investigational medicinal product' has been defined in relation to clinical trials for the purposes of the Clinical Trials Directive mentioned above as being: "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form".

However, this definition was constructed with a specific purpose in mind, that of regulating the performance of clinical trials; hence, the reference to market authorisation. This is clearly unsatisfactory for the general purposes of definition.[2] It would have been better if the subclass of investigational medicinal products had been defined in terms of a more general definition of the class of all medicinal products.

Therefore, we propose the following definition, which describes what a medicinal product is and what it does:

'A medicinal product is one that contains a compound with proven biological effects, plus excipients, or excipients only; it may also contain contaminants. The active compound is usually a drug or prodrug but may be a cellular element. A medicinal product is one that is intended to be taken by or administered to a person or animal for one or more of the following reasons: (i) as a placebo; (ii) to prevent a disease; (iii) to make a diagnosis; (iv) to test for the possibility of an adverse effect; (v) to modify a physiological, biochemical, or anatomical function or abnormality; (vi) to replace a missing factor; (vii) to ameliorate a symptom; (viii) to treat a disease; and/or (ix) to induce anaesthesia.'

The following are notes about this definition.

- The term 'medicine', or the more old-fashioned term 'medicament', are acceptable synonyms for 'medicinal product'. However, although the term 'drug' is often used colloquially to mean a medicinal product (as in 'adverse drug reaction'), it is important to remember the distinction between the drug itself (the active component) and the whole product. For definitive regulatory or legislative purposes the more precise term 'medicinal product' is preferable.

- The term 'pharmaceutical product' is sometimes used, but this excludes some biological products that are not made pharmaceutically.
- 'A compound with proven biological effects' includes chemical compounds, either drugs or prodrugs (which themselves may have no pharmacological activity), racemic mixtures, stereoisomers that may have only adverse effects, or compounds that are used for diagnostic purposes (such as contrast media used by radiologists, including ultrasonographers). This term also includes cellular elements, such as inactivated or attenuated viruses for immunisation, blood products (such as erythrocytes), viruses for gene therapy, and embryonic stem cells.
- 'Contaminants' includes chemical and biological contaminants.
- The definition does not include food additives.
- The definition does not include medicinal products when they are used to probe systems, such as the use of phenylephrine to study baroreceptor reflexes. This is important, because it excludes such products from the terms of the EC Directive on Clinical Trials referred to earlier in this section.[3]

1.2 Pharmaceutical Formulation

A pharmaceutical formulation, also called a 'dosage form', is the form in which a medicinal product is presented, for example as a tablet, capsule, elixir, solution for injection, transdermal formulation, cream, or ointment. The commonly used term, 'preparation', is ambiguous, since it can refer to the pure substance itself (for example, as prepared from a plant) as well as the formulation.

When formulations are classified according to the time over which the active substance is made available to the body, two broad categories can be distinguished: immediate-release formulations and modified-release formulations. Other terms that are subsumed by the term 'modified-release' include sustained-release, slow-release, long-release, controlled-release, timed-release, prolonged-release, and delayed-release.

1.3 Excipient

An excipient can be defined as any material, other than the therapeutically active substances, present in a pharmaceutical formulation. Excipients provide bulk, assist in the manufacture of a formulation (for example, by reducing the stickiness of a powder), control the rate at which a tablet disintegrates, provide a protective coating, inhibit degradation of the active substance during storage, mask the taste of a medicine, provide colouring, and control the rate of release of the medicine. They can cause adverse effects.

2. General Terms Used in Describing Adverse Drug Reactions

2.1 Adverse Reaction and Adverse Effect

The terms 'adverse reaction' and 'adverse effect' refer to the same phenomenon, but an adverse effect is seen from the point of view of the drug, whereas an adverse reaction is seen from the point of view of the patient. The drug causes an 'effect', whereas the patient has a 'reaction'. The term 'adverse effect' is preferable to other terms that are commonly used in a general sense. These include 'toxic effect' or 'side effect', which mean something different (see section 3.2). 'Unwanted effect' is a synonym for 'adverse effect'; however, the definition of adverse drug reaction that we propose excludes very minor unwanted effects.

Adverse effects are either suspected or attributed. If they are attributed to a medicinal product the attribution should ideally be accompanied by a statement of the degree of probability of the attribution (see section 6).

2.2 Adverse Event

The term 'adverse drug effect (or reaction)' must be distinguished from the term 'adverse event (or experience)'. An adverse drug effect is an adverse outcome that can be attributed, with some degree of probability, to an action of a drug. An adverse event is an adverse outcome that occurs while a patient is taking a drug or at some time afterwards but that may or may not be attributable to it. All adverse drug effects are adverse events, but not all adverse

events are adverse drug effects. This distinction is important in clinical trials, in which not all events are necessarily drug induced. In describing adverse outcomes as events rather than (drug-induced) effects, investigators acknowledge that it is not always possible to attribute causality.

We propose the following definition of an adverse event, based on previous definitions:[4,5]

'An adverse event is any abnormal sign, symptom, laboratory test, syndromic combination of such abnormalities, untoward or unplanned occurrence (e.g. an accident or unplanned pregnancy), or any unexpected deterioration in a concurrent illness.'

The term 'adverse drug event' is sometimes used but is confusing for the following reasons. If the cause of an adverse event is not known it remains an (unattributed) adverse event; if the cause is thought to be a drug the adverse event becomes a suspected adverse drug effect; and if the cause is attributed to a medicinal product, the adverse event can be described as an adverse drug effect, often with a stated degree of probability (e.g. probable or possible). But to say 'adverse drug event' implies that the drug has been implicated, which in turn means that the event is described as an adverse drug effect, either suspected or attributed.

The term 'adverse drug event' has been defined as "an injury resulting from medical intervention related to a drug"[6] in order to encompass harms that arise from medication errors as well as conventional adverse drug reactions. If the term were confined to this usage there would be no problem. However, ambiguity arises from its wider use. This can be seen in figure 1, a Venn diagram that shows the relation between adverse events, adverse drug reactions, and medication errors. 'Adverse drug events', as defined by Bates et al.,[6] would encompass adverse drug reactions, whether caused by errors or not, and harm other than adverse drug reactions caused by medication errors (i.e. the areas marked 2, 3 and 4 in figure 1). The confusion that this can cause is illustrated by the advice given in a paper about adverse drug reactions, entitled 'Adverse drug event', in which it was stated that "adverse events should be reported on … yellow [cards]", which refers to the UK regulatory agency's reporting system.[7] Apart from the confusion between adverse events associated with drug therapy and adverse drug reactions, it is suspected adverse reactions that should be reported, not all adverse events.

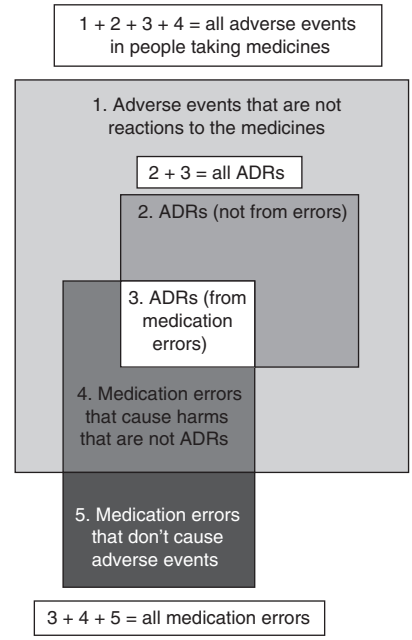

Fig. 1. A Venn diagram showing the relation between adverse events, adverse drug reactions, and medication errors; 'adverse drug events,' as defined by Bates et al.,[6] would encompass areas 2 + 3 + 4. **ADRs** = adverse drug reactions.

2.3 Definition of 'Adverse Drug Reaction'

The WHO's definition of an adverse drug reaction is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function."[8]

This definition has been widely accepted but has defects. One obvious defect is that adverse effects can occur at doses other than those that are used in the way that the definition describes, for example after a test dose. Furthermore, the use of the word noxious excludes adverse effects that may be inconvenient but not harmful.

Laurence[9] has suggested the following definition that specifically excludes minor unwanted reactions (for example, a slight dryness of the mouth), effects that he says should not be dignified with the designation adverse effect: "a harmful or signifi-

cantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis), which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration."

However, these definitions (and others reviewed elsewhere[10]) exclude error as a source of adverse effects.[11] Moreover, they exclude reactions due to contaminants (for example, in herbal medicines) or supposedly inactive excipients in a pharmaceutical formulation. Others, therefore, in the context of adverse events, have used the definition of "an injury resulting from medical intervention related to a drug".[6] But further problems arise from this definition; for instance, the words 'injury' and 'medical' are ambiguous and there is no reason why an intervention should necessarily be medical to cause an adverse effect.

The following definition of an adverse drug reaction, slightly modified from a previous version,[12] obviates these difficulties:

'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.'

The following are notes about this definition.

- 'Appreciably' rules out completely trivial effects but includes anything that the patient detects, which may seem trivial to the doctor but not to the patient. It is better than 'significantly', since the latter courts ambiguity between clinical and statistical significance.
- 'Intervention': an adverse effect can result from the intervention itself rather than the medicinal product (for example, a haematoma from an intramuscular injection); an intervention need not be deliberate. The omission of the word 'medical' removes any implication about who conducts the intervention, for example it might be a doctor, nurse, or herbalist.
- 'Medicinal product' includes inactive excipients and contaminants, as previously defined.
- 'Usually predict hazard': 'usually' because there are occasional exceptions, for example first-dose hypotension from an ACE inhibitor does not necessarily predict hypotension during subsequent therapy.
- 'Alteration' implies either a reduction or an increase in the total dose; for example, if we accept that a loss of effect of a drug is an adverse effect,[13] an increase in dose might be the appropriate treatment.
- 'Dosage regimen': it may be desirable to alter not the dose itself but the formulation, frequency, or duration of treatment.

3. Terms Used in Classifying Adverse Drug Reactions

The history of the classification of adverse drug reactions is summarised in table I.

3.1 The Alphabetic Classification of Adverse Drug Reactions

In 1977, Rawlins and Thompson[17] suggested a division into two types of adverse drug reaction, which they called A and B. Rawlins later listed the clinical features of the two types, stating that type A reactions were predictable and dose dependent and that type B reactions were not,[26] an approach that had been prefigured by Wayne in 1958,[14] Levine in 1973,[15] and Wade and Beeley in 1976.[16] A little later, perhaps appreciating that it was difficult to remember which type of reaction was A and which was B, Rawlins and Thompson invented a mnemonic; they called type A reactions 'augmented' and type B 'bizarre'.[18]

Some of the problems posed by classification into type A and type B reactions become clear when the definitions given by Rawlins and Thomas[27] are carefully examined. Type A reactions, they wrote, "are the result of an exaggerated, but otherwise normal, pharmacological action of a drug given in the usual therapeutic doses … they are usually dose-dependent" and type B reactions "are totally aberrant effects that are not to be expected from the known pharmacological actions of a drug when given in the usual therapeutic doses to a patient whose body handles the drug in the normal way".

There are some difficulties with these definitions. First, type A reactions are said to be '*usually* dose-dependent', implying that some may not be. However, if type A reactions result from an exagger-

Table I. The history of classifications of adverse drug reactions based on dose relatedness and time course

Author(s), date	Classification based on dose relatedness	Classification based on time course
Wayne,[14] 1958	Distinguishes predictable effects ("toxic effects … related to the main action of the drug or to its side effects") and unpredictable effects ("not related to the main or subsidiary pharmacological action of a drug")	
Levine,[15] 1973	Distinguishes dose-related ('toxic' and 'idiosyncratic') reactions from non-dose-related ('allergic') reactions	Distinguishes acute, subacute, and chronic toxic reactions
Wade and Beeley,[16] 1976	Distinguish dose-related and non-dose-related effects	Distinguish long-term and teratogenic effects
Rawlins and Thompson,[17] 1977	Propose two types of reactions: type A and type B (see definitions in section 3.1)	
Rawlins and Thompson,[18] 1981	Add a mnemonic: type A reactions = 'augmented ', type B reactions = 'bizarre'	
Grahame-Smith and Aronson,[19] 1984	Classify types A and B as dose-related and non-dose-related reactions	Add two time-related categories: long-term and delayed
Hoigné et al.,[20] 1990		Distinguish acute, subacute, and latent allergic reactions
Park et al.,[21] 1992		Label the categories of Grahame-Smith and Aronson[19] as: C (long-term) and D (delayed)
Laurence and Bennett,[22] 1992		Split type C into two types: type C (continuous) and type E (end of use)
Ferner and Mann,[23] 1997		Distinguish five different patterns of time course that are useful in diagnosing adverse reactions
Hartigan-Go and Wong,[13] 2000	Add a sixth category: F for failure	
Aronson,[24] 2002	Adds a seventh category: G for genetic/genomic	
Aronson and Ferner,[25] 2003	Distinguish three types of dose-related reactions: toxic, collateral and hypersusceptibility reactions	Distinguish time-dependent and time-independent reactions, with important subtypes

ation of the 'normal' pharmacological action, they should depend on dose. In fact, we argue that all adverse reactions are dose related. Secondly, it is not clear what is meant by a 'normal pharmacological action'. The term implies that there may be, under some circumstances, *abnormal* pharmacological actions. By 'normal' they may mean the action that is usually associated with a therapeutic effect, but even that is problematic (see section 3.2). Thirdly, it is possible for a type A reaction to result from a 'normal pharmacological action', without its being 'exaggerated'. For example, α-adrenoceptor antagonists (α-blockers) produce their therapeutic effect in benign prostatic hyperplasia by a degree of antagonism that in vascular smooth muscle is sufficient to cause hypotension, yet hypotension induced by an α-blocker would presumably be classified as a type A reaction.

Fourthly, the definition of type B reactions does not specify whether they are or are not dose dependent. Indeed, although reactions under this heading are generally regarded as being non-dose dependent,[26] nothing about the definition quoted previously restricts type B reactions in this way. For example, dose-dependent nausea and vomiting due to erythromycin could be classified as a type A reaction as defined, because it is dose related, or as a type B reaction as defined, since its mechanism is neither known nor predictable from its antibacterial (i.e. 'normal') action. In other words, it is not clear whether erythromycin-induced nausea should be classified as type A or type B according to the definitions. This is clearly unsatisfactory and highlights another difficulty – that an adverse reaction that is at first classified as being of type B might have to be reclassified as being of type A when its pharmacological basis and dose relation become known. Finally, not all adverse reactions can be comfortably accommodated within this classification. For example, corticosteroid-induced osteoporosis depends not only on dose but also on duration of therapy, and tumours induced by chemotherapy with alkylating agents depend on dose but are greatly delayed. These distinctions have implications for drug development and the management (monitoring, prevention, diagnosis, and treatment) of adverse reactions.

Nevertheless, the A/B classification has persisted and partly in response to the problems it poses has been extended during the 25 years since it was first proposed (table I). First, Grahame-Smith and Aronson[19] modified it by formally replacing the labels 'type A' and 'type B' with the labels 'dose-related' and 'non-dose related'. They also added two time-related categories, 'long-term' and 'delayed', which others subsequently labelled as types C and D.[21] Some further divided type C (long term) into type C (continuous) and type E (end of use, i.e. withdrawal).[22] Subsequently, sixth and seventh categories, F for failure and G for genetic/genomic, have been proposed.[13,24]

However, although it solves some of the problems of the original A/B classification, the extended classification has other major problems. For example, there is an overlap among the categories. This overlap takes two forms. First, despite the fact that it is logical to distinguish short-term reactions (types A and B) from long-term reactions (types C and E) or delayed reactions (type D), types A and B have been respectively classified as dose related or not, while the dose relatedness of the other types has not been considered. Furthermore, the sixth category, F for failure, is not a mechanistic category but an outcome that could arise from reactions in at least some of the other categories. The seventh category, G for genetic/genomic, refers to one form of susceptibility that is more or less important in all types of adverse reactions. This illustrates the seductiveness of the mnemotechnics associated with the alphabetic classification; one could readily add other categories along these lines, such as H for hypersensitivity, but doing so would not resolve the problems.

Rawlins and Thomas[27] have suggested that there is no need to introduce categories beyond the two originally proposed in 1977, arguing that "additional classes [do not] assist in understanding either the mechanisms of adverse drug reactions or their management". If the original classification into two types, A and B, subsumed all types of adverse reactions, we would agree. However, some adverse reactions are not well classified in this way and we also argue that the distinction between dose-related and non-dose-related reactions, as originally defined, is a false one. Furthermore, the extended classification, which tackles some of the deficien-

cies of the A/B classification, introduces other problems and is also unsatisfactory.

3.2 Dose Relatedness of Adverse Drug Reactions

The A/B classification assumes that there are adverse effects that are not dose related. However, it is a basic pharmacological principle that effects of drugs involve interactions between chemical entities and are, therefore, subject to chemical laws, including the law of mass action. This implies that all drug effects, beneficial or adverse, including immunological reactions, are dose related; indeed, many well known immunological reactions are demonstrably dose or concentration related, such as:

- hay fever in response to changing pollen counts;[28]
- the immunogenic response to hepatitis B vaccine;[29]
- desensitisation by the use of increasing doses of antigen (e.g. cephalosporins);[30]
- type IV hypersensitivity skin reactions.[31]

For example, both the induction and subsequent amplification of skin hypersensitivity to dinitrochlorobenzene increase linearly with the logarithm of the sensitising dose, as does the response to a subsequent challenge.[31] The hydralazine-induced, lupus-like syndrome, whose mechanism is not understood but may be immunological, is also dose related.[32] The use of a test dose (e.g. of antitetanus antiserum) to establish the likelihood of immediate type hypersensitivity implies that it also depends on dose, since the test dose is high enough to cause the reaction but low enough to limit its severity.

As mentioned earlier, type B reactions are defined as "totally aberrant effects that are not to be expected from the known pharmacological actions of a drug when given in the usual therapeutic doses". If all adverse reactions are dose related, the labelling of some reactions as non-dose dependent[26] is misleading, and this definition implies that it is the dose or concentration at which an adverse effect occurs that defines it to be of either type A or B, i.e. not the dose relatedness of the effect but the position of the dose-response curve. However, the concept of a 'usual therapeutic dose' is also flawed, for several reasons.

- There is often wide variability in responsiveness to a given dose of a drug.[33]
- For some drugs, doses vary according to indication, for example the effective dosage of vitamin D in dietary deficiency is 10 μg/day, compared with 2500 μg/day in renal osteodystrophy. The effective dosage of clonidine in preventing migraine may be as low as 100 μg/day, compared with up to 1200 μg/day in hypertension. The usual dosage of bromocriptine in cyclic benign breast disease is 5 mg/day, compared with up to 40 mg/day in Parkinson's disease.
- Dose responsiveness can change from time to time, even in the same individual, for example if there is tolerance; this is most obvious in opioid use.

It is sometimes argued that the doses required for pharmacological effects are orders of magnitude greater than those required for immunological effects, so that a distinction can be made on those grounds. But that is not true. For example, the dose of *Botulinum* toxin needed to treat torticollis is of the order of 25pg per muscle and a daily dose of 250ng of alfacalcidol can be sufficient to treat vitamin D deficiency. By comparison, doses of the order of micrograms are used as immunising antigens. For example, *Haemophilus influenzae* b vaccine contains 10μg of antigen per dose, hepatitis B vaccine contains 20μg per dose and typhoid vaccine 25μg per dose. Even in molar terms there are wide variations in these doses.

For this reason we have proposed classifying adverse effects by the concentration at which they occur relative to the therapeutic concentration in an individual,[25] as follows.

- Toxic effects: adverse effects that occur at supratherapeutic concentrations.
- Collateral effects: effects that occur at standard therapeutic concentrations.
- Hypersusceptibility reactions: reactions that occur at subtherapeutic doses in susceptible patients.

This is illustrated in figure 2 and summarised in table II.

A toxic effect is one that occurs as an exaggeration of the desired therapeutic effect. For example,

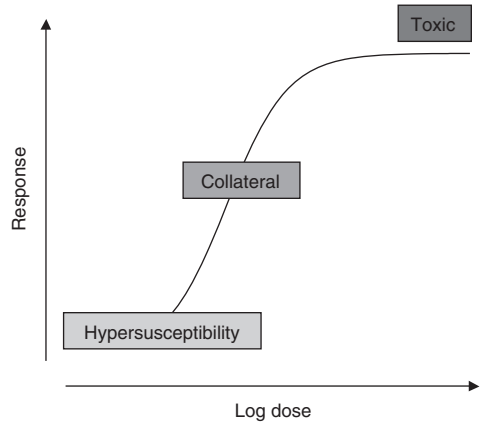

Fig. 2. A schematic representation of a log concentration-response or dose-response curve that shows the concentrations or doses at which toxic, collateral, and hypersusceptibility reactions occur.

syncope due to a nitrate is a toxic effect – it occurs by the same mechanism as the therapeutic effect (vasodilatation).

Collateral effects generally occur in a tissue other than that in which the therapeutic action is sought, although not necessarily in another organ. They can occur either: (i) through the same pharmacological effect as the one whereby the therapeutic action is produced (for example, colour vision disturbance from sildenafil); or (ii) through a distinct pharmacological effect (for example, a dry mouth due to an anticholinergic effect of a tricyclic antidepressant). We use the term 'collateral effects' for adverse effects that occur at standard therapeutic concentrations, because the term 'side effects' is often colloquially used to refer to all adverse effects. Furthermore, a WHO definition says ambiguously that a side effect "is related to the pharmacological properties of the drug".[10] In addition, side effects can be beneficial, and some authors have defined side effect as being any unintended effect of medicinal therapy, whether good or bad. Because of the potential confusion, it may be best not to use the term 'side effect' at all. The term 'adverse drug effect (or reaction)' encompasses all types of deleterious effects; it makes no assumptions about mechanism, evokes no ambiguity, and avoids the risk of misclassification.

Hypersusceptibility reactions can be immune related or not and the term 'hypersusceptibility' avoids implications about whether the mechanism is immunological (also see section 3.4 on susceptibility to adverse effects).

3.3 Time Relatedness of Adverse Drug Reactions

To concentrate simply on the dose relatedness of adverse effects is to ignore another important aspect, their time relatedness. In an earlier paper[25] we have distinguished time-dependent effects from time-independent effects.

3.3.1 Time-Independent Reactions

Time-independent reactions occur at any time during a course of therapy, independent of the duration of the course. They typically occur:

- when the amount of drug being administered changes by a pharmaceutical mechanism (e.g. by altered availability from a pharmaceutical formulation);
- when the concentration of the drug at the site of action changes by a pharmacokinetic mechanism (e.g. digoxin toxicity when renal function worsens);
- when the pharmacological response is altered by a pharmacodynamic mechanism without a change in concentration at the site of action (e.g. digoxin toxicity in association with potassium depletion).

When such a reaction occurs, the delay before it occurs may be affected by the pharmacokinetics of the drug, but that is not an aspect of its time dependency as it is defined here.

3.3.2 Time-Dependent Reactions

Time-dependent reactions are of six subtypes: rapid, first dose, early, intermediate, late, and delayed.

Rapid reactions: Rapid reactions occur when a drug is administered too rapidly, for example the red man syndrome with vancomycin.[34] They are typically toxic reactions.

First-dose reactions: First-dose reactions occur after the first dose of a course of treatment and not necessarily thereafter. They are typically hypersusceptibility reactions. Examples include hypotension after the first dose of an ACE inhibitor[35] and type I allergic reactions. In the latter, the reaction is observed after the first dose of a course, whether or not

Table II. The dose, time, and susceptibility (DoTS) classification of adverse drug reactions (ADRs)[22]

ADR characteristic	Examples	Implications
A. Dose-related (concentration-related) reactions		
Type of reaction		
Toxic reactions		
Occur at supratherapeutic concentrations	Syncope due to nitrates; digitalis toxicity	Reduce the dose or withdraw therapy
Collateral reactions		
Occur at standard therapeutic concentrations		
(i) Through the same pharmacological effect as the therapeutic action	Colour vision disturbance from sildenafil	Generally unavoidable; tolerate, treat, or withdraw
(ii) Through a distinct pharmacological effect	A dry mouth due to an anticholinergic effect of a tricyclic antidepressant	
Hypersusceptibility reactions		
Occur at subtherapeutic concentrations in susceptible patients	Penicillin allergy	Avoid
B. Time-related effects		
Type of reaction		
Time independent		
Due to a change in dose or concentration (pharmaceutical effects)	Toxicity due to increased systemic availability	Beware of changing formulations of some drugs (e.g. modified-release formulations of lithium)
Due to a change in dose or concentration (pharmacokinetic effects)	Digoxin toxicity due to renal insufficiency	Forewarn the patient; monitor carefully throughout treatment; alter dose when pharmacokinetics change (e.g. renal insufficiency); avoid interacting drugs
Occurs without a change in dose (pharmacodynamic effects)	Digitalis toxicity due to hypokalaemia	Forewarn the patient; monitor carefully throughout treatment; avoid precipitating (pharmacodynamic) factors; avoid interacting drugs
Time dependent		
Rapid (due to rapid administration)	Red man syndrome (vancomycin)	Administer slowly
	Hypertension (digitalis)	
	Hypotension (iodipamide)	
First dose (of a course)	Hypotension (α_1 adrenoceptor antagonists and ACE inhibitors)	Take special precautions for the first dose
	Type I hypersensitivity reactions	Careful history taking; if a reaction occurs, avoid re-exposure; counsel the patient
Early (abates with repeated exposure)	Adverse reactions that involve tolerance (e.g. nitrate-induced headache)	Monitor during the early stages; give appropriate reassurance; expect adverse effects if strategies to avoid tolerance are adopted
Intermediate (risk increases at first, then diminishes)	Venous thromboembolism (antipsychotic drugs)	Monitoring not needed after the high-risk period unless susceptibility changes; withdraw drug if a reaction develops
	Hypersensitivity reactions type II, type III and type IV	
Late (risk increases with time)	Osteoporosis (corticosteroids)	Assess baseline function; forewarn the patient; monitor periodically during prolonged treatment
	Tardive dyskinesia (dopamine receptor antagonists)	

Continued next page

Table II. Contd

ADR characteristic	Examples	Implications
	Retinopathy (chloroquine)	
	Tissue phospholipid deposition (amiodarone)	
	Withdrawal syndromes: opioids, benzodiazepines, hypertension (clonidine and methyldopa), myocardial infarction (β-adrenoceptor antagonists)	Withdraw slowly; forewarn the patient; replace with a longer-acting drug if withdrawal is not possible
Delayed	Carcinogenesis (ciclosporin, diethylstilbestrol)	Avoid or screen; counsel or forewarn the patient
	Teratogenesis (thalidomide)	
C. Susceptibility factors		
Source of susceptibility		
Genetic	Porphyria	Screen for abnormalities; avoid specific drugs
	Suxamethonium chloride (succinylcholine) sensitivity	
	Malignant hyperthermia	
	Cytochrome P450 (CYP) isozyme polymorphisms	
Age	Neonates (chloramphenicol)	Adjust doses according to age
	Elderly people (hypnosedatives)	
Sex	Alcohol intoxication	Use different doses in men and women
	Mefloquine, neuropsychiatric effects	
	ACE inhibitors, cough	
	Lupus-like syndrome	
Physiology altered	Phenytoin in pregnancy	Alter dose or avoid
Exogenous factors	Drug interactions	Alter dose or avoid co-administration
	Interactions with food (e.g. grapefruit juice with drugs cleared by CYP3A4)	
Disease	Renal insufficiency (e.g. lithium)	Screen for abnormalities; avoid specific drugs; use reduced doses
	Hepatic cirrhosis (e.g. morphine)	

there has been a record of previous exposure – 30% of those who develop anaphylaxis with penicillin have no such record.[36] We regard a previous sensitising exposure as causing a change in susceptibility (see section 3.4).

Early reactions: Early reactions occur early in treatment then abate with continuing treatment. They are typically collateral effects. These are reactions to which patients develop tolerance (e.g. nitrate-induced headache).

Intermediate reactions: Intermediate reactions occur after some delay; however, during longer-term therapy the risk falls. If after a certain time there is no reaction, there is little or no risk that it will occur later. They can be collateral or hypersusceptibility reactions. Examples are allergic reactions of type II (e.g. thrombocytopenia due to quinine), type III (e.g. interstitial nephritis with penicillins), and type IV (e.g. cutaneous allergy due to antihistamines), and the ampicillin/amoxicillin pseudoallergic rash.[37] Non-allergic reactions of this type include the increased risk of neutropenia with carbimazole[38] and of venous thromboembolism with antipsychotic drugs.[39] We believe that intermediate reactions occur in populations of individuals with different susceptibilities. Those at high risk have the reaction and stop taking the drug. Those at low risk do not have the reaction and can be regarded as 'healthy survivors'. Thus, the population risk appears to fall with time.

Late reactions (including withdrawal reactions): Late reactions occur rarely or not at all at first, but the risk increases with continued or repeated exposure. They are typically collateral effects. Examples include many of the adverse effects of glucocorticoids and tardive dyskinesia with dopamine receptor antagonists. Withdrawal reactions are late reactions that occur when, after prolonged treatment, a drug is withdrawn or its effective dose is reduced. They include opiate and benzodiazepine withdrawal syndromes, hypertension after withdrawal of clonidine or methyldopa, and acute myocardial infarction after β-adrenoceptor antagonist (β-blocker) withdrawal.

Delayed reactions: Delayed reactions are observed some time after exposure, even if the drug is withdrawn before the reaction appears. They are typically collateral reactions. Examples are carcinogenesis (e.g. vaginal adenocarcinoma in women whose mothers took diethylstilbestrol during pregnancy) and teratogenesis (e.g. phocomelia due to thalidomide).

3.4 Susceptibility to Adverse Drug Reactions

The risk of an adverse reaction differs among different members of an exposed population, and this is partly determined by differing susceptibility. Susceptibility in this context is the capacity to have an adverse reaction. As discussed in section 3.2 we define hypersusceptibility reactions as adverse reactions that occur at subtherapeutic doses in susceptible patients. Although reasons for hypersusceptibility may be unknown, there are several recognised types.[25] These include:

- genetic factors
- age
- sex
- physiological factors (e.g. pregnancy)
- endogenous factors (e.g. other drugs and foods)
- diseases.

Hypersusceptibility is a general term that can be used to describe increased susceptibility to an adverse reaction, whatever the mechanism. Several other terms have been used, including idiosyncrasy, intolerance, and hypersensitivity. Widely different definitions of these terms can be found in different sources.

3.4.1 Idiosyncrasy

Idiosyncrasy has been defined as:

- an individual's hypersensitivity to a drug or other substance that is ingested or inhaled, or that otherwise comes into contact with the body;[40]
- a response that is qualitatively different from that normally seen, generally due to a single gene inheritance;[9]
- an individual's hypersensitivity to a drug or other substance that is ingested or inhaled or otherwise comes into contact with the body;[41]
- a response that is qualitatively different from that normally seen, generally due to a single gene inheritance;[9]
- an inherent qualitatively abnormal reaction;[42,43]
- an abnormal susceptibility to some drug, protein or other agent that is peculiar to the individual.[44]

However, it is wrong to equate idiosyncrasy and hypersensitivity, which has a distinct meaning (see sections 3.4.1 and 3.4.3), and not all forms of reactions that are termed idiosyncratic are due to single gene disorders. For example, although some authors describe type B reactions as idiosyncratic,[21] others have argued that this is not appropriate,[43] which is a position with which we agree. Furthermore, the juxtaposition of the terms 'susceptibility' and 'peculiar to an individual' is tautologous in this context. We believe that the term idiosyncrasy has no useful place in descriptions of adverse drug reactions. Idiosyncrasy is merely an ill-defined expression of unusually increased susceptibility. Individual susceptibility should be the touchstone.

3.4.2 Intolerance

Intolerance has been defined as:

- a greater than expected quantitative response to a dose of a drug … an individual with a non-allergic *qualitatively* abnormal response has an idiosyncrasy;[9]
- sensitivity, as to a drug.[44]

However, the term 'tolerance' has a specific pharmacological meaning, namely "diminished sensitivity to a drug resulting from previous exposure to that drug or a related drug (cross-tolerance)".[9] The term 'intolerance' also suggests that a patient is unable to tolerate an adverse effect, which is not necessarily so, and it adds nothing beyond what is implied in the term 'adverse reaction'. Intolerance is

also sometimes confusingly equated with hypersensitivity. We believe that the term 'intolerance' has no useful place in descriptions of adverse reactions to medicinal products, although it may have a role in describing adverse reactions to foods.[45]

3.4.3 Hypersensitivity

Hypersensitivity has been defined as:

- an allergic reaction to a drug or other stimulus;[9]
- a qualitatively normal response that occurs at a lower dose or concentration of the drug than usual;[9]
- a state of altered reactivity in which the body reacts with an exaggerated or inappropriate immune response to what is perceived to be a foreign substance;[44]
- [a reaction that is] characterised by the fact that a marked adverse bodily response may be evoked by some specific substance or agent that (in similar amounts) has no such effect on most individuals.[41]

In the context of adverse drug reactions, the term hypersensitivity may be best restricted to hypersusceptibility reactions of immunological origin, i.e. classical type 1 immune reactions.

The dose, time, and susceptibility (DoTS) classification of adverse drug reactions, based on the dose (or concentration) at which effects occur, the time course of the effect, and the susceptibility of the patient, is outlined in table II.

4. The Seriousness of an Adverse Drug Reaction

In the UK, the Committee on Safety of Medicines asks that prescribers report all suspected adverse reactions to new and some intensely monitored medicines (marked in the British National Formulary with an inverted black triangle) and all serious suspected reactions to established medicines. It is, therefore, important to define what is meant by a serious adverse reaction. Combining previous definitions,[10] we propose the following definition:

"Any untoward medical occurrence that at any dose: (i) results in death; or (ii) is life threatening; or (iii) requires or prolongs hospital admission; or (iv) results in significant disability/incapacity; or (v) requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or (vi) is a cancer or a congenital anomaly; or (vii) is any medical event that would be regarded as serious if it had not responded to acute treatment."

5. The Intensity of an Adverse Drug Reaction

The seriousness of an adverse drug reaction discussed in section 4 is a measure of the extent to which the reaction can or does cause harm. In contrast, the intensity (severity) of an adverse drug reaction is a measure of the extent to which the adverse effect develops in an individual. For example, ventricular tachycardia or hepatic impairment of any severity is serious, while discoloration of the urine by rifampicin, even if very pronounced (i.e. intense or severe), is not serious. Severity and seriousness are, therefore, different concepts. A severe reaction need not be serious.

The terms 'trivial', 'mild', 'moderate', and 'severe' are often used to describe the intensity of an adverse reaction. However, there are no satisfactory definitions of these terms and using any one of them to describe a particular adverse reaction implies a value judgement, which may differ from patient to patient and from prescriber to prescriber. To illustrate this, the following ranges of definitions from different sources can be considered.[9,46-48]

- Trivial: nuisance value only.
- Mild: some interference with patient function; slightly bothersome; symptoms do not alter patient's normal functioning.
- Moderate: symptoms are marked, but involvement of vital organ systems is moderate; bothersome, interferes with activities; symptoms produce some degree of impairment to function but are not hazardous, uncomfortable, or embarrassing.
- Severe: fatal or life threatening; lowers the patient's life expectancy and there is severe impairment of a vital organ system, even if transient; prevents regular activities; symptoms definitely hazardous to well being; significant impairment of function or incapacitation.

None of these definitions is satisfactory, not least because of the difficulty of objective quantification. Furthermore, some of the terms used to define 'se-

Table III. A proposed classification of the intensity of an adverse drug reaction, based on the need to change the dosage regimen of the offending drug and the treatability of the reaction

Grade	Change in dosage regimen of the offending drug	Treatability of the reaction
1	No change in dosage regimen required	A. No treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment
2	Altered dosage regimen required or desirable	A. No other treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment
3	Withdrawal required or desirable	A. No other treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment

vere' actually mean 'serious'. However, there are two types of classification that are more useful: one based on whether a change in the dosage regimen of the offending drug is required[49] and one based on the extent to which the adverse reaction is treatable.[47] Based on these two ideas we propose a grading of intensity (severity) that avoids terms such as mild, moderate, and severe (table III). In this classification, the response to treatment of the adverse effect, if treatment is required, can be assessed before or after any change in dosage regimen of the offending drug, but that should be stated.

6. Defining the Causal Probability of Adverse Drug Reactions

When an adverse event has been attributed to a drug, it is helpful to state the causal probability (sometimes called the causality). Two questions arise: how likely is it that the drug can cause the adverse effect (the general problem) and, if it can, how likely is it that it was the cause in this case (the specific problem)?

6.1 Causal Probability of a Single Report

There are no satisfactory definitions of the terms that are used in stating causal probabilities in single cases, and different proposed systems use different collections of terms of varying complexity, such as:

- definite, probable, and possible;[49]
- definite, probable, possible, conditional, and doubtful;[50]
- certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable.[51]

However, for practical purposes, it is usually impossible in specific cases to definitively demonstrate a causal association between a drug and an adverse event, not least because demonstration requires repeated exposure to the drug, which is precluded by serious adverse effects. Words such as 'definite' and 'certain' are therefore too absolute. The word 'unlikely' is also unhelpful, since it attributes an adverse effect to a drug while at the same time implying that the attribution is doubtful. We prefer not to use these terms at all and propose terms such as probable, possible, and unclassifiable, as in the following system.[52]

- Probable (category A).
- Possible (category B).
- Unclassified (category O).

However, the definitions of probable and possible given by the proponents of this classification involve vague terms such as 'assume', 'accept the possibility', 'uncertain', and 'doubtful'. The definition of unclassifiable is simpler: a reaction is termed unclassifiable if there is insufficient evidence to assign a probability or if there are conflicting data.[52] However, if it is not possible to know how to assign a probability it will be equally impossible to decide unclassifiability. Although attempts have been made to overcome the difficulties by using decision algorithms[5,53-57] and Bayesian techniques,[55,56] such methods have major limitations.[58]

The extent of this problem is illustrated by the degree of variability in the meanings that people attribute to words that are used to express probability. For example, the following mean percentage (standard deviation) chances were assigned to the words probable and possible in one study:[59]

- Probable: 77 (12).
- Possible: 43 (21).

In the same study highly variable percentages were also assigned to different degrees of probability.

- High probability: 87 (7).
- Moderate probability: 61 (15).
- Low probability: 17 (20).

Furthermore, in other studies widely different percentages (standard deviations) were assigned to the same words.[60] For example, the term 'possible' was assigned a chance of 43% (21) in one study[59] and 27% (17) in another.[60] It is therefore better to communicate probabilities in percentages (e.g. 5%) or the corresponding fractions (0.05). The problem of communicating such information to non-professionals has not been solved, but techniques include comparisons with other risks (e.g. the annual risk of dying in a road accident is 1 in 8000, by murder is 1 in 100 000, or by lightning is 1 in 10 000 000),[61] visual analogues,[62] and other forms of analogy,[63] such as tossing a coin to illustrate a 50% chance or considering the relative chances of injuring yourself by jumping from different storeys in a building.

6.2 Causal Probability of a Drug/Adverse Effect Association Based on Series of Reports

Risk can be defined as "the probability that a particular adverse outcome occurs during a given quantum of exposure to hazard".[64] 'Quantum' here refers to such variables as the duration of exposure or the amount of drug given. In some cases the risk of an adverse reaction in the general population (i.e. its causal probability in the general sense) can be calculated. For example, in a randomised placebo-controlled trial the incidence of a particular adverse event in those taking the drug can be compared with the incidence in those taking the placebo, and the probability of the association can be calculated. When enough data from homogeneous trials are available a systematic review can do the same. Based on data of this sort, one can calculate the number needed to harm from the inverse of the absolute risk.[24] For example, if an adverse event occurs in 5% of those who take a drug for 1 year and 3% of those who take placebo, the absolute risk of harm due to the drug is 2% and the number needed to harm is 100/2 or 50. In other words, if you treat 50 people with the drug for 1 year, on average one more will experience the adverse event than if you had used a placebo; confidence intervals about that estimate can also be calculated.

Methods are also being developed for assessing the probability that an observable event is one of the adverse effects of a drug on the basis of a series of individual reports of an apparent association, including Bayesian techniques for application to databases of anecdotal reports.[65-67] The Bayesian Confidence Propagation Neural Network method has been tested as a tool for finding new adverse drug reactions in the Uppsala database. It has a positive predictive value of slightly under 50% but a negative predictive value of approximately 85%.[68]

Some insight into how other methods might be devised comes from analysing how the frequency of an adverse event in patients taking a drug and the background frequency of the same event together determine the ease of proving the possible association[69] (table IV). For example, if a drug is associated with an adverse event that is otherwise rare, there is a high likelihood that the event is an adverse effect and in such cases a few anecdotal reports would be

Table IV. The relation between the frequency of an adverse event in patients taking a drug and the background frequency of the same event together in determining the ease of proving the possible association

Incidence of an event in patients taking the drug	Background incidence of the event	Example	Ease of proving the association
Common	Rare	Phocomelia due to thalidomide	Easy: clinical observation
Rare	Rare	Aspirin (acetylsalicylic acid) and Reye's syndrome	Less easy: clinical observation
Common	Common	ACE inhibitors and cough	Difficult: large observational study
Uncommon	Moderately common	HRT and breast carcinoma	Very difficult: large trial
Rare	Common	None known	Impossible

HRT = hormone replacement therapy.

enough to substantiate a likely association. An example is the attribution of Fanconi syndrome to outdated tetracyclines.[70] At the other end of the spectrum, if a drug is uncommonly associated with an adverse event that is otherwise common, anecdotal reports will not be helpful in establishing the association. In such cases large trials or observational studies are required. Of course, this is a purely qualitative analysis and it is not clear if a useful comparable quantitative version could be developed. But if it were, it would have to be based on actual frequencies of events rather than verbal expressions of such frequencies, which are unreliable (see section 7).

7. Defining the Frequency of Adverse Drug Reactions

Risks and frequencies of adverse effects are often discussed at the same time. However, although the risk of an adverse effect in a population is the same as its frequency in that population, the risk in an individual need not be. It is possible for an individual, because of some susceptibility, to have a high risk of an adverse effect that has a low frequency in the population. It is, therefore, best to separate notions of individual risk and population risk or frequency.

Table V. Interpretation of words used to indicate frequencies

Word	Interpretation (range of mean percentages)	References
Invariably/always	91–100	59,60,71-74
Almost always	85–94	71-74
Normally	71–81	59,71,72
Usually	70–84	71-73
Common(ly)	56–69	71,73,75
More often than not	64	71
Often	42–71	71-74
Frequent(ly)	36–72	60,71,73,75
Not infrequently	24–35	71,73
Sometimes	11–33	59,71,72,74
Occasionally	17–21	71-73
On occasion	12	71
Infrequently	12–14	73
Seldom	7–8	73
Rare(ly)	0.5–9	71-75
Very rare(ly)	0.8–3	74
Almost never	2	60
Exceptionally	0.4–1	74
Never	0–2	60,71-74

Many attempts have been made to quantify the expressions, such as 'common(ly)' and 'rare(ly)', that are used to denote frequencies of events in populations. Some of the results of such investigations are shown in table V, from which it is clear that none of the terms that are used can be assigned a specific frequency. The data in this table are simply the ranges of means from different studies. In most cases the variability around those means was even greater in individual studies than the range of means shown in the table.

Many factors influence the interpretations of words such as these. Consider, for example, the expression 'rare(ly)'. In one study, recently qualified doctors (interns) assigned to 'rarely' a mean estimate of 5.2% and consultants (attending physicians) assigned a mean estimate of 8.7%;[73] age and experience may have affected these judgements. In another study, 59% of the doctors thought that 'rare' meant <1 in 1000 when it referred to adverse effects of β-adrenoceptor antagonists, but 62% of the same doctors thought that it meant between 1 in 100 and 1 in 1000 when it referred to the adverse effects of antihistamines.[75] The severity or seriousness of the expected adverse effect presumably influenced these judgements.

Thus, in professional communications, frequencies should be stated in numbers (e.g. 1 in 1000). However, an arbitrary verbal scale of population risks/frequencies has been suggested (table VI)[76] and is a useful shorthand.

8. Definitions of Specific Adverse Reactions

In addition to definitions of general terms, adverse effects themselves (for example, anaphylaxis, apnoea, and tachyarrhythmia) require specific definitions. Several dictionaries have been developed to deal with this problem and others have been incorporated into them. They are:

- ADROIT: the Adverse Drug Reactions On-line Information Tracking medical dictionary;[77]
- COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms;

Table VI. A verbal scale for describing frequencies, with some examples of causes of deaths that have those frequencies (reproduced from Calman,[76] with permission from BMJ Publishing Group)

Verbal description of frequency	Numerical estimate of frequency	Examples of causes of death with that frequency
High	>1 : 100	Gastrointestinal adverse effects of antibacterials
Moderate	1 : 100–1 : 1000	Smoking 10 cigarettes/day
Low	1 : 1000–1 : 10 000	Influenza, road accident
Very low	1 : 10 000–1 : 100 000	Leukaemia
Minimal	1 : 100 000–1 : 1 000 000	Polio immunisation
Negligible	<1 : 1 000 000	Struck by lightning

- WHO-ART: the WHO Adverse Reaction Terminology;[78]
- ICD: the International Classification of Disease, now in its 10th edition (ICD-10);
- SNOMED: the Systematized Nomenclature of Human and Veterinary Medicine;[79]
- a series of papers by the Council for International Organisations of Medical Sciences (CIOMS), started in 1992[80] and published fully in 1999;[81]
- MedDRA: Medical Dictionary for Regulatory Activities.[82]

Constant updating of such dictionaries is necessary. For example, the term 'anaphylactoid reaction', as defined by the CIOMS,[80] has been superseded in a proposed new classification of allergic drug reactions[83] in which anaphylactic drug reactions are defined as allergic and non-allergic anaphylactic reactions, the former being further subdivided according to whether they are IgE mediated or not. This classification implies that the term "anaphylactoid reaction" should be replaced by the term "non-allergic anaphylactic reaction".

A detailed discussion of these dictionaries is beyond our scope here. For further information, see Stephens et al.[10]

9. The Balance of Benefit and Harm in Drug Therapy

Drugs are prescribed because of their potential benefit to the patient, but in every case this is accompanied by a risk of harm; before prescribing the potential benefits should ideally be weighed against the potential harm. This is commonly described as assessing the benefit to risk ratio. However, a benefit is an *actual* outcome, while a risk is a *chance* of an outcome[84] and the two are non-comparable.

It is therefore better to relate benefit to harm. Furthermore, since it is generally not possible to derive measures of benefit and harm that can be combined into an arithmetic ratio, it is better to talk about the balance of benefit and harm or the benefit-harm balance. More specifically, the benefit-harm balance is a function of the seriousness of the problem to be treated, the efficacy and safety of the drug to be used, and the efficacy and safety of other available drugs. This is illustrated in table VII.

Measures of the benefit-harm balance include the number needed to treat and number needed to harm[24] and quality-adjusted life-years (QALYs) gained through benefit compared with QALYs lost through harm.[85,86]

10. Signals

A signal in pharmacovigilance has been defined as "reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented."[87] It is a hint that an association may be causal and requires formal investigation. A signal

Table VII. The factors that contribute to an assessment of the benefit-harm balance in drug therapy. A drug that fulfills the criteria in the top line has a very high benefit-harm balance, while one that fulfills the criteria in the bottom line has a very low benefit-harm balance. Most drugs lie somewhere between the two extremes

Seriousness of the indication	Efficacy of the drug	Adverse reactions		Other drugs		Benefit-harm balance
		seriousness	frequency	efficacy	safety	
Life threatening	High	Trivial	Rare	Poor	Poor	Very high
Trivial	Poor	Serious	Frequent	Good	Good	Very low

might be reported in a single report to a regulatory or monitoring authority, in an anecdotal report in a journal, or in a report of one or more events in a clinical trial. However, a single report may constitute noise, i.e. an observed but non-causal association, and several reports may be required before a causal signal can be distinguished from noise through proper investigation. An example of an inappropriate signal was the report that 'Debendox' ('Bendectin') was teratogenic,[88] an association that was subsequently disproved in large studies.[89] For this reason, a note to the above definition of a signal states that "usually more than a single report is required to generate a [causal] signal, depending on the seriousness of the event and the quality of the information."[90]

The term 'signal generation' that is sometimes used is inappropriate. Signals are detected and reported, not generated. Or rather, they are generated by giving medicines to people, not by sifting data.

11. Conclusion

The nomenclature surrounding drug safety needs to be clear and unambiguous, so that patients, prescribers, manufacturers and regulators can all understand each other. In particular, it needs to make clear how adverse events and drug therapy are related to one another, how they are best classified, and their frequency, intensity, and seriousness. Medication errors, which can lead to adverse drug reactions, require their own clear definitions and mechanistic classification.

In this article, instead of creating definitions from scratch as is commonly done, we have taken the novel approach of critically examining definitions that have been proposed or widely used and have formulated new or modified definitions based on a logical appraisal of their merits and demerits. We hope that these definitions will lead to discussion that will allow a corpus of satisfactory definitions to be widely agreed.

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References

1. Buetow SA, Sibbald B, Cantrill JA, et al. Appropriateness in health care: application to prescribing. Soc Sci Med 1997; 45: 261-71
2. Aronson JK. What is a clinical trial? Br J Clin Pharmacol 2004; 58: 61-3
3. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Off J Eur Commun 2001; L121: 34-44 [online]. Available from URL: http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf [Accessed 2003 Sep 26]
4. Inman WH. Postmarketing surveillance of adverse drug reactions in general practice. I: search for new methods. BMJ (Clin Res Ed) 1981; 282: 1131-2. II: Prescription-event monitoring at the University of Southampton. BMJ (Clin Res Ed) 1981; 282: 1216-7
5. Kramer MS, Leventhal JM, Hutchinson TA, et al. An algorithm for the operational assessment of adverse drug reactions. I: Background, description, and instructions for use. JAMA 1979; 242: 623-32
6. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. ADE Prevention Study Group. JAMA 1995; 274: 29-34
7. Dunn N. 10-minute consultation: adverse drug event. BMJ 2003; 326: 1018
8. World Health Organization. International drug monitoring: the role of national centres. Technical Report Series No 498. Geneva: WHO, 1972
9. Laurence D, editor, Carpenter J, contributor. A dictionary of pharmacology and allied topics. Amsterdam: Elsevier, 1998
10. Stephens MBD, Talbot JCC, Routledge PA, editors. The detection of new adverse drug reactions. 4th ed. London: Macmillan, 1998: 32-44
11. Ferner RE, Aronson JK. Errors in prescribing, preparing, and giving medicines: definition, classification, and prevention. In: Aronson JK, editor. Side effects of drugs. Annual 22. Amsterdam: Elsevier, 1999
12. Edwards IR, Aronson JK. Adverse drug reactions: definitions, classification, diagnosis, management, surveillance. Lancet 2000; 356: 1255-60
13. Hartigan-Go KY, Wong JQ. Inclusion of therapeutic failures as adverse drug reactions. In: Aronson JK, editor. Side effects of drugs. Annual 23. Amsterdam: Elsevier, 2000: xxvii-xxxiii
14. Wayne EJ. Problems of toxicity in clinical medicine. In: Walpole AL, Spinks A, editors. The evaluation of drug toxicity. London: J & A Churchill Ltd, 1958: 1-11
15. Levine RR. Factors modifying the effects of drugs in individuals. In: Pharmacology: drug actions and reactions. Boston (MA): Little, Brown and Co, 1973: 261-91
16. Wade OL, Beeley L. Adverse reactions to drugs. 2nd ed. London: William Heinemann Medical Books Ltd, 1976: Chapter II
17. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford: Oxford University Press, 1977: 44
18. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. 2nd ed. Oxford: Oxford University Press, 1981: 11
19. Grahame-Smith DG, Aronson JK. The Oxford textbook of clinical pharmacology and drug therapy. Oxford: Oxford University Press, 1984: 134
20. Hoigné R, Jaeger MD, Wymann R, et al. Time pattern of allergic reactions to drugs. Agents Actions Suppl 1990; 29: 39-58

21. Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. Br J Clin Pharmacol 1992; 34: 377-95
22. Laurence DR, Bennett PN. Clinical pharmacology. Edinburgh: Churchill Livingstone, 1992: 121-2
23. Ferner R, Mann RD. Drug safety and pharmacovigilance. In: Page C, Curtis MJ, Sutter MC, et al., editors. Integrated pharmacology. 1st ed. London: Mosby, 1997: 83-90
24. Aronson JK. Evidence-based medicine and the principles of drug therapy. Chapter 2. In: Haslett C, Chilvers ER, Boon NA, et al., editors. 19th ed. Davidson's textbook of medicine. Edinburgh: Churchill Livingstone, 2002
25. Aronson JK, Ferner RE. Joining the DoTS: classifying adverse drug reactions by dose responsiveness, time course, and susceptibility. BMJ 2003; 327: 1222-5
26. Rawlins MD. Clinical pharmacology: adverse reactions to drugs. BMJ (Clin Res Ed) 1981; 282: 974-6
27. Rawlins MD, Thomas SHL. Mechanisms of adverse drug reactions. In: Davies DM, Ferner RE, De Glanville H, editors. Davies's textbook of adverse drug reactions. 5th ed. London: Chapman & Hall Medical, 1998: 40
28. Frenz DA. Interpreting atmospheric pollen counts for use in clinical allergy: allergic symptomology. Ann Allergy Asthma Immunol 2001; 86: 150-7
29. Troisi CL, Heiberg DA, Hollinger FB. Normal immune response to hepatitis B vaccine in patients with Down's syndrome: a basis for immunization guidelines. JAMA 1985; 254: 3196-9
30. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med 2001; 345: 804-9
31. Friedmann PS, Moss C, Shuster S, et al. Quantitative relationships between sensitising dose of DNCB and reactivity in normal subjects. Clin Exp Immunol 1983; 53: 709-15
32. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. BMJ (Clin Res Ed) 1984; 289: 410-2
33. Smith SE, Rawlins MD. Variability in human drug response. London: Butterworths, 1973
34. Wallace MR, Mascola JR, Oldfield EC. Red man syndrome: incidence, etiology and prophylaxis. J Infect Dis 1991; 164: 1180-5
35. Alderman CP. Adverse effects of the angiotensin-converting enzyme inhibitors. Ann Pharmacother 1996; 30: 55-61
36. Saxon A, Beall GN, Rohr AS, et al. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987; 107: 204-15
37. Geyman JP, Erickson S. The ampicillin rash as a diagnostic and management problem: case reports and literature review. J Fam Pract 1978; 7: 493-6
38. Li KL, Huang HS, Wang PW, et al. Agranulocytosis associated with anti-thyroid drug in patients with Graves' thyrotoxicosis: report of 11 cases. Changgeng Yi Xue Za Zhi 1991; 14: 168-73
39. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. Lancet 2000; 356: 1219-23
40. Hektoen L. Allergy or anaphylaxis in experiment and disease. JAMA 1912; 58: 1081-8
41. Simpson J, Weiner E, editors. The Oxford English Dictionary. 2nd ed. Oxford: Oxford University Press, 1989
42. Rosenheim ML, Moulton R, editors. Sensitivity reactions to drugs. Oxford: Blackwells Scientific Publications, 1958: 4
43. Hoigné RV. Should "idiosyncrasy" be defined as equivalent to "type B" adverse drug reactions? Pharmacoepidemiol Drug Saf 1997; 6: 213
44. Dorland's Illustrated Medical Dictionary. 30th ed. Philadelphia (PA): Saunders, 2003
45. David TJ. Adverse reactions and intolerance to foods. Br Med Bull 2000; 56: 34-50
46. Venulet J. Monitoring adverse reactions to drugs. In: Jucken E, editor. Progress in drug research. Basle: Berghausen Verlag, 1977
47. Tangrea JA, Adrianza ME, McAdams M. A method for the detection and management of adverse events in clinical trials. Drug Inf J 1991; 25: 63-80
48. Assenzo JR, Sho VS. Use of statistics in the analysis of side-effect data from clinical trials of psychoactive agents. Prog Neuropsychopharmacol Biol Psychiatry 1982; 6: 543-50
49. Grohmann R, Rütter E, Sassim N, et al. Adverse effects of clozapine. Psychopharmacology 1989; 99: S101-4
50. Karch FE, Lasagna L. Adverse drug reactions. JAMA 1975; 234: 1236-41
51. World Health Organization. Letter MIO/372/2(A). Geneva: World Health Organization, 1991
52. Meyboom RHB, Royer RJ. Causality classification at pharmacovigilance centres in the European Community. Pharmacoepidemiol Drug Saf 1992; 1: 87-97
53. Hutchinson TA, Leventhal JM, Kramer MS, et al. An algorithm for the operational assessment of adverse drug reactions. II: Demonstration of reproducibility and validity. JAMA 1979; 242: 633-8
54. Leventhal JM, Hutchinson TA, Kramer MS, et al. An algorithm for the operational assessment of adverse drug reactions. III: Results of tests among clinicians. JAMA 1979; 242: 1991-4
55. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability for adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45
56. Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. Clin Pharmacol Ther 1995; 58: 692-8
57. Stephens MDB. The diagnosis of adverse medical events associated with drug treatment. Adverse Drug React Acute Poisoning Rev 1987; 1: 1-35
58. Meyboom RH, Hekster YA, Egberts AC, et al. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997; 17: 374-89
59. Bryant GD, Norman GR. Expressions of probability: words and numbers [letter]. N Engl J Med 1980; 302: 411
60. Kong A, Barnett GO, Mosteller F, et al. How medical professionals evaluate expressions of probability. N Engl J Med 1986; 315: 740-4
61. Calman KC, Royston GDH. Risks language and dialects. BMJ 1997; 315: 939-42
62. Paling J. Strategies to help patients understand risks. BMJ 2003; 327: 745-8
63. Edwards A. Communicating risk through analogies [letter]. BMJ 2003; 327: 749
64. Royal Society Study Group. Risk assessment. London: The Royal Society, 1983
65. Lindquist M, Edwards IR, Bate A, et al. From Association to Alert: a revised approach to international signal analysis. Pharmacoepidemiol Drug Saf 1999; 8: S15-25
66. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998; 54: 315-21
67. Orre R, Lansner A, Bate A, et al. Bayesian neural networks with confidence estimations applied to data mining. Comput Stat Data Analysis 2000; 34: 473-93
68. Lindquist M, Ståhl M, Bate A, et al. A retrospective valuation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. Drug Saf 2000; 23: 533-42
69. Jick H. The discovery of drug-induced illness. N Engl J Med 1977; 296: 481-5

70. Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. BMJ (Clin Res Ed) 1982; 284: 249-52
71. Kenney RM. Between never and always. N Engl J Med 1981; 305: 1097-8
72. Toogood JH. What do we mean by "usually"? [letter]. Lancet 1980; I: 1094
73. Roberts DE, Gupta G. How medical professionals evaluate expressions of probability [letter]. N Engl J Med 1987; 316: 550
74. Marion MN, Simon P. Signification des adverbes utilisés pour indiquer la frequence des effets secondaires d'un medicament. Thérapie 1984; 39: 4762-3
75. Mapes REA. Verbal and numerical estimates of probability in therapeutic contexts. Soc Sci Med 1979; 13A: 277-82
76. Calman KC. Cancer: science and society and the communication of risk. BMJ 1996; 313: 799-802
77. Wood SM, Coulson R. Adverse Drug Reactions On-line Information Tracking (ADROIT). Pharm Med 1993; 7: 203-13
78. Brown EG. Effects of coding dictionary on signal generation: a consideration of use of MedDRA compared with WHO-ART. Drug Saf 2002; 25: 445-52
79. Wang AY, Sable JH, Spackman KA. The SNOMED clinical terms development process: refinement and analysis of content. Proc AMIA Symp 2002: 9
80. Council for International Organizations of Medical Sciences. Basic requirements for the use of terms for reporting adverse drug reactions. Pharmacoepidemiol Drug Saf 1992; 1: 39-45
81. Bankowski Z, Bruppacher R, Crusius I, Gallagher J, Kremer G, Venulet J, editors. Reporting adverse drug reactions: definitions of terms and criteria for their use. Geneva: CIOMS, 1999
82. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999; 20: 109-17
83. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56: 813-24
84. Herxheimer A. Benefit, risk and harm. Aust Presc 2001; 24: 18
85. Sandercock P, Berge E, Dennis M, et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Health Technol Assess 2002; 6: 1-112
86. Hunink MG, Bult JR, de Vries J, et al. Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. Med Decis Making 1998; 18: 337-46
87. World Health Organization. Safety of medicines: a guide to detecting and reporting adverse drug reactions [online]. Available from URL: http://www.who.int/medicines/library/qsm/who-edm-qsm-2002-2/esd_safety.pdf [Accessed 2003 Sep 26]
88. Orme ML'E. The Debendox saga. BMJ (Clin Res Ed) 1985; 291: 918-9
89. Mazzotta P, Magee LA. A risk-benefit assessment of pharmacological and nonpharmacological treatments for nausea and vomiting of pregnancy. Drugs 2000; 59: 781-800
90. Delamothe T. Reporting adverse drug reactions. BMJ 1992; 304: 465

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