

## Adverse drug reactions

# Adverse drug reactions: definitions, diagnosis, and management

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We define an adverse drug reaction as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.” Such reactions are currently reported by use of WHO’s Adverse Reaction Terminology, which will eventually become a subset of the International Classification of Diseases. Adverse drug reactions are classified into six types (with mnemonics): dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Timing, the pattern of illness, the results of investigations, and rechallenge can help attribute causality to a suspected adverse drug reaction. Management includes withdrawal of the drug if possible and specific treatment of its effects. Suspected adverse drug reactions should be reported. Surveillance methods can detect reactions and prove associations.

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects. The risk of such effects ranges from near zero (with, for example, nystatin and hydroxocobalamin) to high (with, for example, immunosuppressive or antineoplastic drugs). Here we define the terms used to describe adverse effects, explain their classification, and discuss the general ways in which they can be diagnosed, managed, and monitored.

### Definitions

WHO’s definition of an adverse drug reaction, which has been in use for about 30 years, 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”.<sup>1</sup> However, in its use of the word “noxious” (defined in the *Oxford English Dictionary* as “injurious, hurtful, harmful”), this definition is vague; does it, for example, include all adverse reactions, no matter how minor? Such inclusiveness would defeat surveillance systems as they currently operate. Laurence’s definition<sup>2</sup> specifically excludes minor unwanted reactions (eg, a slight dryness of the mouth): “A harmful or significantly 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<sup>3</sup>) exclude error as a source of adverse effects.<sup>4</sup> Moreover, they exclude reactions due to contaminants (eg, in herbal medicines) or supposedly inactive excipients in a formulation. Indeed, there is a case for talking about adverse reactions to medicines or medicaments, rather than adverse drug reactions, since medicinal products contain ingredients other than active principles. Others, in the context of adverse events, have used the definition of “an injury resulting from medical intervention related to a drug”.<sup>5</sup> But other 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.

We therefore propose the following definition of an adverse drug reaction: “An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

The term “adverse effect” is preferable to other terms such as “toxic effect” or “side effect”. A toxic effect is one that occurs as an exaggeration of the desired therapeutic effect, and which is not common at normal doses. For example, a headache due to a calcium antagonist is a toxic effect—it occurs by the same mechanism as the therapeutic effect (vasodilatation). A toxic effect is always dose-related. On the other hand, an unwanted side effect occurs via some other mechanism and may be dose-related or not. For example, the dose-related anticholinergic effect of a tricyclic antidepressant is a side effect, since this action is not associated with the therapeutic effect; similarly, non-dose-related anaphylaxis with a penicillin is a side effect. A WHO definition says ambiguously that a side effect “is related to the pharmacological properties of the drug”;<sup>3</sup> however, this definition was formulated to include side effects that, although not the main aim of therapy, may be beneficial rather than harmful. Such an effect may or may not occur through the pharmacological action for which the drug is being used. For example, treating hypertension with a  $\beta$ -blocker may, by  $\beta$ -blockade, also relieve the patient’s angina, a beneficial side effect; alternatively, a depressed patient with irritable bowel syndrome may incidentally benefit from the anticholinergic side effect of a tricyclic antidepressant as well as from its antidepressant action. The term “adverse effect” encompasses all unwanted effects; it makes no assumptions about mechanism, evokes no ambiguity, and avoids the risk of misclassification.

The terms “adverse reaction” and “adverse effect” are interchangeable, except that 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. However, the terms “adverse effect” and “adverse reaction” must be distinguished from “adverse event”. An adverse effect is an

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| Type of reaction                        | Mnemonic   | Features   | Examples  | Management   |
|---|------------|--|---|--|
| <b>A: Dose-related</b>                  | Augmented  | <ul style="list-style-type: none"> <li>Common</li> <li>Related to a pharmacological action of the drug</li> <li>Predictable</li> <li>Low mortality</li> </ul>          | <ul style="list-style-type: none"> <li>Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs</li> <li>Side effects: Anticholinergic effects of tricyclic antidepressants</li> </ul>                          | <ul style="list-style-type: none"> <li>Reduce dose or withhold</li> <li>Consider effects of concomitant therapy</li> </ul> |
| <b>B: Non-dose-related</b>              | Bizarre    | <ul style="list-style-type: none"> <li>Uncommon</li> <li>Not related to a pharmacological action of the drug</li> <li>Unpredictable</li> <li>High mortality</li> </ul> | <ul style="list-style-type: none"> <li>Immunological reactions: Penicillin hypersensitivity</li> <li>Idiosyncratic reactions: Acute porphyria, Malignant hyperthermia, Pseudoallergy (eg, ampicillin rash)</li> </ul> | <ul style="list-style-type: none"> <li>Withhold and avoid in future</li> </ul>   |
| <b>C: Dose-related and time-related</b> | Chronic    | <ul style="list-style-type: none"> <li>Uncommon</li> <li>Related to the cumulative dose</li> </ul>   | <ul style="list-style-type: none"> <li>Hypothalamic-pituitary-adrenal axis suppression by corticosteroids</li> </ul>  | <ul style="list-style-type: none"> <li>Reduce dose or withhold; withdrawal may have to be prolonged</li> </ul>             |
| <b>D: Time-related</b>                  | Delayed    | <ul style="list-style-type: none"> <li>Uncommon</li> <li>Usually dose-related</li> <li>Occurs or becomes apparent some time after the use of the drug</li> </ul>       | <ul style="list-style-type: none"> <li>Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol)</li> <li>Carcinogenesis</li> <li>Tardive dyskinesia</li> </ul>  | <ul style="list-style-type: none"> <li>Often intractable</li> </ul>  |
| <b>E: Withdrawal</b>                    | End of use | <ul style="list-style-type: none"> <li>Uncommon</li> <li>Occurs soon after withdrawal of the drug</li> </ul>   | <ul style="list-style-type: none"> <li>Opiate withdrawal syndrome</li> <li>Myocardial ischaemia (<math>\beta</math>-blocker withdrawal)</li> </ul>  | <ul style="list-style-type: none"> <li>Reintroduce and withdraw slowly</li> </ul>  |
| <b>F: Unexpected failure of therapy</b> | Failure    | <ul style="list-style-type: none"> <li>Common</li> <li>Dose-related</li> <li>Often caused by drug interactions</li> </ul>  | <ul style="list-style-type: none"> <li>Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers</li> </ul>  | <ul style="list-style-type: none"> <li>Increase dosage</li> <li>Consider effects of concomitant therapy</li> </ul>         |

SSRIs=serotonin-selective reuptake inhibitors.

Table 1: **Classification of adverse drug reactions**

adverse outcome that can be attributed to some action of a drug; an adverse event is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it. This distinction is important, for example, in clinical trials, in which not all events are necessarily drug-related. In describing adverse outcomes as events rather than (drug-related) effects, investigators acknowledge that it is not always possible to ascribe causality. This distinction is also tacitly acknowledged in the definition proposed above.

In addition to definitions of these general terms, specific definitions of adverse effects themselves (for example,

anaphylaxis, apnoea, arrhythmia) have been formulated in a series of papers by the Council for International Organizations of Medical Sciences, starting in 1992,<sup>6</sup> and have been used in computerised databases. Some other terms that may be useful are given in panel 1.

The currently accepted international terminology for reporting of adverse drug reactions is WHO's Adverse Reaction Terminology (WHO-ART).<sup>7</sup> This terminology is hierarchical, and links system or organ classes to three types of terms: broad "high-level" terms; more specific and disease-related or symptom-related "preferred" terms; and finally the frequently reported alternative "included" term and true synonyms. This terminology is intended for use alongside the general disease terminology—the International Classification of Diseases (ICD). Work is being undertaken to link these classifications, so that WHO-ART will become a subset of ICD.

Another initiative is the medical terminology for drug regulatory authorities (MedDRA).<sup>8</sup> This terminology includes historical terms from WHO-ART, ICD9, and COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms; used in the past by the US Food and Drug Administration). MedDRA is currently being promoted commercially and is accepted by the European Union, the USA, and Japan. However, compatibility with ICD and WHO-ART is no longer complete, since MedDRA has more terms and another level in its hierarchy, so that the links between terms may be different from those in WHO-ART, even when there is correspondence in individual terms. MedDRA also has many more low-level terms, which are designed to help in the coding of published case reports; they may do this, but the inclusion of imprecise and unscientific terms could present challenges in using data derived from them. For example, the link between a term such as "immune reaction" and more precise terms is difficult. We look forward to better use of information technology to allow recording and use of text data, so that nothing is lost between the narrative report and what is stored and searchable in a database of reports.

Recent publications have given severity gradings to specific reaction types (eg, the Common Toxicity Criteria; <http://ctep.info.nih.gov/CTC3/ctcctinfo.htm>). Although these may be useful in some settings, such gradings do not

#### Panel 1: **Some adverse drug reaction terms and their definitions**

##### **"Unexpected adverse reaction"**

- An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug

##### **"Serious adverse effect"**

- Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening

- Cancers and congenital anomalies or birth defects should be regarded as serious

- Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious

- The term "severe" is often used to describe the intensity (severity) of a medical event, as in the grading "mild", "moderate", and "severe"; thus a severe skin reaction need not be serious

##### **"Adverse event/adverse experience"**

- Any untoward occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment

##### **"Signal"**

- Reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented

- Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information

have international acceptance. Furthermore, many of them have discontinuity in their logic; for example, is toxic epidermal necrolysis a severe skin rash or is it a distinct entity?

### Classification

The forerunner of the modern pharmacological classification of adverse drug reactions distinguished dose-related and non-dose-related reactions, which were first called type A and type B, respectively.<sup>9</sup> Later, for mnemonic purposes, they were labelled “Augmented” and “Bizarre”.<sup>10</sup> Subsequently, two further types of reaction were added: reactions related to both dose and time, and delayed reactions,<sup>11</sup> later labelled types C and D.<sup>12</sup> The last of these categories can be split into two: time-related reactions and withdrawal effects. More recently, a sixth category has been proposed: unexpected failure of therapy.<sup>13</sup> This classification is shown in table 1, with examples of adverse drug reactions in each category and notes on their management.

Of course, it is not always possible to classify an adverse drug reaction into one of these categories, but that is in the nature of classification. As more becomes known about the mechanisms of specific adverse drug effects, this classification will be revised further and classification of currently unclassifiable reactions will become easier.

### Diagnosis and attribution of causality

The diagnosis of an adverse drug reaction is part of the broader diagnosis in a patient. If a patient is taking medicines, the differential diagnosis should include the possibility of an adverse drug reaction. The first problem is to find out whether a patient is taking a medicinal product, including: over-the-counter formulations; products that may not be thought of as medicines (such as herbal or traditional remedies, recreational drugs, or drugs of abuse); and long-term treatments that the patient may forget (such as oral contraceptives).

The next step is to find out whether the effect could be due to a medicine. If the patient is taking several medicines, the problem is to distinguish which, if any, is causative. This problem is complex, because some of the patient's complaints might be due to other diseases or to one or more of the drugs. There are many formal methods for assigning probability of causation to a suspected adverse drug reaction.<sup>14,15</sup>

#### Timing

The time relation between the use of the drug and the occurrence of the reaction should be assessed. Are they plausibly linked? For example:

- Does the reaction occur or get worse as the dose of the drug reaches steady state or when the steady-state dose is increased (for dose-related reactions)?
- Does the reaction abate or disappear as the dose of the drug is reduced or the drug is withdrawn (for dose-related reactions)?
- If a drug interaction is suspected, does the timing of introduction or withdrawal of the interacting drug fit?
- If there are features of an allergic reaction, has the patient previously been exposed? Lack of previous exposure does not rule out an allergic reaction, but previous exposure is consistent with such a reaction.
- If the effect is a congenital abnormality, did drug exposure occur at the appropriate gestational time?
- If the effect is a tumour, was the time lag sufficiently long for the tumour to have grown? The answer to this will depend on a knowledge of tumour kinetics.

### Panel 2: Causality assessment of suspected adverse drug reactions

#### Certain

- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals
- The response to withdrawal of the drug (dechallenge) should be clinically plausible
- The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary

#### Probable/likely

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge)
- Rechallenge information is not required to fulfil this definition

#### Possible

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals
- Information on drug withdrawal may be lacking or unclear

#### Unlikely

- A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations

#### Conditional/unclassified

- A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined

#### Unassessable/unclassifiable

- A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified

#### Pattern recognition

The pattern of the adverse effect may fit the known pharmacology or allergy pattern of one of the suspected medicines, or of chemically related or pharmacologically related compounds. Some patterns are pathognomonic or nearly so; for example, in a patient taking digoxin, a combination of heart block and an ectopic arrhythmia will almost certainly be due to the drug. However, this information should not be used to rule out an association, particularly with a new medicine, since an adverse drug reaction may not be known, or even predictable, from the pharmacology. For instance, corticosteroids, commonly used to suppress immune responses, can cause allergic reactions.

Next, one should consider the background frequency of the event and how often it is associated with drugs. Headache is relatively common, so its association with a medicine may be by chance. In contrast, aplastic anaemia has a low background incidence and is often associated with medicines; it is therefore more likely to be an adverse drug reaction.

#### Investigations

Investigations (such as plasma concentration measurement, biopsies, and allergy tests) can aid diagnosis, establish baselines for organ function (eg, liver, kidney, or thyroid function), and provide a means for monitoring what happens after changes in therapy. They may also rule

out alternative diagnoses. Sometimes it is wise to establish baseline functions at the start of therapy in anticipation of an adverse drug reaction; for example, baseline thyroid function tests are routinely ordered before giving amiodarone, which can not only cause thyroid disease but which also alters thyroid function tests, even when thyroid function is normal, making interpretation difficult. In other cases, such anticipation is of no help; for example, the white-cell count during carbimazole or methimazole therapy does not predict neutropenia, which can be diagnosed only when it occurs.

Finally, rechallenge with the drug should be considered, particularly if the patient is likely to benefit directly from the knowledge gained.

At the end of this exercise, it should be possible to attribute causality. Numerous schemes for classification of causality have been proposed and are used in different countries.<sup>16</sup> We prefer the scheme outlined in panel 2.<sup>3,17</sup>

## Management

Rapid action is sometimes important because of the serious nature of a suspected adverse drug reaction, for example anaphylactic shock. Emergency treatment and withdrawal of all medicines is occasionally essential, in which case cautious reintroduction of essential medicines should be considered. Otherwise, using clinical benefit-risk judgment, together with help from investigations, one decides which medicine or medicines should be withdrawn as a trial. A problem immediately arises if one or more of the medicines is essential to the patient. If the culprit is fairly clear, a benefit-risk decision needs to be taken about the need for the drug (are there equally effective substitutes that are unlikely to produce the same adverse drug reaction?), the severity of the reaction, and its potential for treatment. If several medicines could be causative, the non-essential medicines should be withdrawn first, preferably one at a time, depending on the severity of the reaction. If the reaction is likely to be dose-related, dose reduction should be considered. Many prescribers unnecessarily withhold a drug when interactions are suspected, rather than adjusting the dose.

The patient should be observed during withdrawal. The waiting period will vary, depending on the rate of elimination of the drug from the body and the type of pathology. For example, urticaria usually disappears quickly when the drug is eliminated, whereas fixed psoriatic skin reactions can take weeks to resolve. If the patient is clearly getting better, in keeping with the

prediction, alternative medicines for the basic disease can be introduced if necessary. If the patient is not doing well after withdrawal of the first drug, the next most likely culprit should be considered, and the process repeated. On the other hand, the patient may be suffering through being deprived of the medicine withheld. In that case, either another suitable drug should be substituted (remembering the possibility of cross-sensitivity), or the same drug should be tried at a lower dosage (for a dose-related reaction). The latter approach should be tried if more than one drug was withheld, for instance if an interaction was suspected or if the seriousness of the reaction made it wise to withhold several possible drugs. Reintroduce apparently essential medicines one at a time, starting with the one least likely to be the culprit.

If the patient cannot manage without a medicine that has caused an adverse reaction, provide symptomatic relief while continuing the essential treatment. For example, severe nausea and vomiting are routinely treated symptomatically in patients receiving anti-cancer drugs. However, when treating an adverse drug reaction, it is important not to introduce more medicines than are essential. Always have a clear therapeutic objective in mind, do not treat for longer than is necessary, and review the patient regularly and look for ways to simplify management.

## Surveillance

Surveillance methods for drug reactions, and population methods for proving associations are summarised in table 2.<sup>18–20</sup> Outside of formal surveillance systems, all health-care professionals have a responsibility to inform their colleagues about clinically important adverse drug reactions that they detect, even if a well-recognised or causal link is uncertain. Information on what has happened and how the diagnosis has been made should be forwarded to a national centre with responsibility for giving general information about drugs and for taking regulatory action. National centres send this information to the WHO worldwide database. This global information is analysed by the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre), now with artificial intelligence in the form of a Bayesian Confidence Propagation Neural Network, which allows the analysis of all the variables in a report against the background information contained in the WHO database of over 2 million reports.<sup>18</sup> This work supports the review of information in all member national centres around the

| Method  | Advantages                                     | Disadvantages  |
|---|--|--|
| Anecdotal reporting (eg, in journals)   | Simple; cheap                                  | Relies on individual vigilance and astuteness; may only detect relatively common effects |
| Voluntary organized reporting* (doctors, pharmacists, pharmaceutical companies) | Simple   | Under-reporting; reporting bias by "bandwagon" effect                                    |
| Intensive event monitoring  | Easily organised                               | Selected population studied for a short time   |
| Cohort studies  | Can be prospective; good at detecting effects  | Very large numbers required; very expensive  |
| Case-control studies  | Excellent for validation and assessment        | Will not detect new effects; expensive   |
| Case-cohort studies   | Good for studying rare effects with high power | As for cohort and case-control studies; complex calculations                             |
| Population statistics   | Large numbers can be studied                   | Difficult to coordinate; quality of information may be poor; too coarse                  |
| Record linkage  | Excellent if comprehensive                     | Time-consuming; expensive; retrospective; relies on accurate records                     |
| Meta-analysis   | Uses data that have already been obtained      | Need to obtain unpublished data; heterogeneity of different studies                      |

\*Including computerised systems involving, for example, WHO's monitoring programme,<sup>18</sup> the Committee on Safety of Medicines' yellow card system,<sup>19</sup> and the Food and Drug Administration's Adverse Drug Reaction file system.<sup>20</sup>

Table 2: Surveillance methods for adverse drug reactions and methods of proving associations<sup>11</sup>



world (currently 59) and an international expert review panel.

### Future developments

The work of the WHO monitoring programme in Uppsala is described in detail elsewhere.<sup>21</sup> The programme also supports the European Pharmacovigilance Research Group, which has allowed regulators and drug-safety specialists from a variety of European countries to come together to plan coordinated drug-safety exercises. Initiatives like these may pave the way for much more logical development and investigation of drug safety signals worldwide. Among the developments planned for the WHO programme are:

- An extension of the method of Bayesian artificial neural networks for the analysis of large amounts of data, in the hope of detecting hitherto unrevealed risk factors for the development of drug-related ailments
- Improvements in the classification systems of traditional herbal remedies
- Methods for improving communications in pharmacovigilance, as set out in the Erice declaration<sup>22</sup>
- Cooperation with organisations interested in developing early signals of significance, including the International Society for Pharmacoepidemiology, which is specifically interested in the science of pharmacovigilance, and the Council for International Organizations of Medical Sciences, which is pivotal in bringing interested parties together to mount various collaborative projects.

Clinical pharmacology has a very exciting future, because of possibilities of interfering with disease processes at ever more basic and specific levels. Knowledge of the human genome will allow us to predict susceptibility to an increasing number of diseases, and drug-induced disease will also be better understood as we gain knowledge of genetic influences on drug pharmacokinetics and pharmacodynamics: we already use phenotyping and genotyping to predict some drug problems related to drug metabolism. Further genomic developments will allow us to develop predictive tests for the actions of drugs, including adverse drug reactions, holding out the possibility of more accurate tailoring of therapy to the individual.

As we accumulate more and more information on drug responses, we must not lose sight of the sobering fact that about half the cases of drug-related injury are from potentially avoidable adverse drug reactions.<sup>23,24</sup>

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