Drug Saf (2013) 36:147–153
DOI 10.1007/s40264-013-0019-9

SPECIAL ARTICLE

Distinguishing Hazards and Harms, Adverse Drug Effects and Adverse Drug Reactions

Implications for Drug Development, Clinical Trials, Pharmacovigilance, Biomarkers, and Monitoring

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Published online: 16 February 2013

Abstract The terms 'adverse drug effects' and 'adverse drug reactions' are commonly used interchangeably, but they have different implications. Adverse drug reactions arise when a compound (e.g. a drug or metabolite, a contaminant or adulterant) is distributed in the same place as a body tissue (e.g. a receptor, enzyme, or ion channel), and the encounter results in an adverse effect (a physiological or pathological change), which results in a clinically appreciable adverse reaction. Both the adverse effect and the adverse reaction have manifestations by which they can be recognized: adverse effects are usually detected by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological) or by clinical investigations (e.g. endoscopy, cardiac catheterization), and adverse reactions by their clinical manifestations (symptoms and/or signs). This distinction suggests five scenarios: (i) adverse reactions can result directly from adverse effects; (ii) adverse effects may not lead to appreciable adverse reactions; (iii) adverse reactions can occur without preceding adverse effects; (iv) adverse effects and reactions may be dissociated; and (v) adverse effects and reactions can together constitute syndromes. Defining an adverse drug reaction as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product" suggests a definition of an adverse drug effect: "a potentially harmful effect resulting from an intervention related to the use of a medicinal product, which constitutes a hazard and may or may not be associated with a clinically appreciable adverse reaction and/or an abnormal laboratory test or clinical investigation, as a marker of an adverse reaction."

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1 The Contrast Between Adverse Effects and Adverse Reactions

The terms 'adverse drug effects' and 'adverse drug reactions' are commonly used interchangeably. However, there is a distinct difference, which suggests that different definitions of the two terms are necessary.

The distinction between the two terms is made clear by considering how adverse drug reactions arise:

- … an **E**xtrinsic moiety (e.g. a drug or metabolite, a contaminant or adulterant) …
- … encounters an **I**ntrinsic moiety (e.g. a tissue protein, such as a receptor, ion channel, or enzyme) …
- … the two being **D**istributed in the same place …
- … and the encounter results in an adverse effect (the **O**utcome) …
- … which results in an adverse reaction (the **S**equela).

(This descriptive system has been designated EIDOS, from the initials of its component parts [1].)

Adverse effects and adverse reactions have different manifestations by which they can be recognized: adverse effects are usually detected by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological) or by clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterization), adverse reactions by their clinical manifestations (symptoms and/or signs).

I know of no previous discussion of this distinction, nor of any previous attempt to define adverse effects in contrast to adverse reactions. For example, when Yu et al. searched 33 websites looking for definitions of medication

safety-related terms, they found 25 different terms with 119 definitions; the term 'adverse effect' was not among them [2].

1.1 An Illustrative Example

An adverse effect, which is initiated by an action of a drug at the molecular level, can be described at any level at which it occurs—molecular, cellular, tissue, or organ. For example (Fig. 1), at the molecular level, glucocorticoids bind to glucocorticoid receptors, thus modifying the synthesis of many proteins at the cellular level in bone, including, for example, osteocalcin; at the tissue level, this, and other effects, leads to bone demineralization, which is expressed as osteoporosis at the organ level. However, the adverse effect of osteoporosis, whose laboratory manifestation is abnormal dual-energy X-ray absorptiometry, is not an adverse reaction; it is rather a hazard for the true adverse reaction, which is bone fracture, whose manifestations are pain, tenderness, and immobility. The adverse reaction is what happens at the level of the appreciable symptomatic hurt or organ damage caused.

That this distinction is important is demonstrated by the fact that osteoporosis, an adverse *effect* of corticosteroids, does not closely predict the risk of a fracture, the adverse *reaction*, in patients taking glucocorticoids [3]. Thus, the proper endpoint when measuring the beneficial effects of bisphosphonates in patients taking glucocorticoids is the rate of fractures (the adverse reaction) and not the degree of osteoporosis (the adverse effect). As another example, there is evidence that antiepileptic drugs are associated with an increased risk of fractures, but this is not predicted by bone mineral density [4].

Abnormal laboratory tests that are not accompanied by symptoms or signs are not adverse reactions or even adverse effects, but markers of adverse effects. This distinction is thus relevant to biomarkers and surrogate endpoints and is reflected in the definitions of those terms. A biomarker is "a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [5]. A surrogate endpoint is "a biomarker intended to substitute for a clinical endpoint", the latter being "a characteristic or variable that reflects how a patient feels, functions, or survives" [6]. Thus, biomarkers are analogous to adverse effects and surrogate endpoints to adverse reactions.

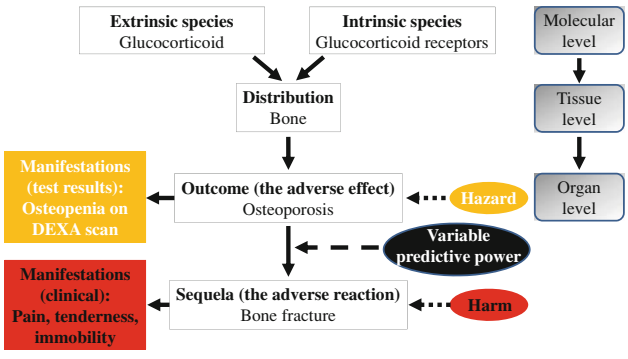

Fig. 1 Fracture as an adverse reaction to glucocorticoids; osteoporosis is the adverse effect. *DEXA* dual energy X-ray absorptiometry

1.2 A Taxonomy of Adverse Events

This analysis does not alter the definition of an adverse event, which is "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" [7]. However, it suggests a taxonomy of adverse events, as shown in Table 1. Adverse events that are attributable to a medicinal product can be of three types:

1. Adverse effects that cause functional impairment or pathological damage.
2. Laboratory and investigational markers of such adverse effects.
3. Adverse reactions (harms) that manifest as clinical signs or symptoms.

2 Relations Between Adverse Effects and Adverse Reactions

This analysis suggests five categories of relations between adverse effects and adverse reactions (summarized in Table 2).

2.1 The Adverse Effect Leads Directly to Appreciable Harm

In most cases, or at least most recognizable cases, adverse effects lead to appreciably harmful or unpleasant outcomes, i.e. adverse reactions. Indeed, it is often only when an adverse reaction occurs that we realize that it has been preceded by adverse effects. An example, QT interval prolongation associated with torsade de pointes due to antiarrhythmic drugs, is shown in Fig. 2. There is a variable link between the adverse effect and the adverse reaction. The former does not necessarily predict the latter, and susceptibility factors, such as poor left ventricular function and hypokalaemia, increase the likelihood that QT interval prolongation will result in torsade de pointes [8].

Table 1 A taxonomy of adverse events that are attributable to a medicinal product

Adverse effects (functional impairment or pathological damage)	Laboratory and investigational markers of adverse effects	Adverse reactions (harms)
Molecular effects (e.g. receptor stimulation)	Biochemistry (e.g. liver function tests)	Whole body reactions
Cellular effects (e.g. inhibition of protein synthesis)	Haematology (e.g. full blood count)	● Symptoms (primary or secondary)
Tissue effects (e.g. atrophy)	Pathology (e.g. histology)	● Signs (primary or secondary)
Organ effects (e.g. impaired function)	Microbiology (e.g. viral antibodies)	
	Immunology (e.g. tissue antibodies)	
	Radiology (e.g. MRI scans)	
	Physiology (e.g. cardiology, neurology)	
	Endoscopy (e.g. gastrointestinal, respiratory, urological)	

Adverse effects (left-hand column) can be due to functional impairment or pathological damage; 'impairment' implies a physiological change (e.g. a change in sympathetic nervous system function or a change in enzyme or transporter activity); 'damage' implies a pathological change (e.g. hypertrophy, atrophy, a change in apoptosis)

MRI magnetic resonance imaging

Table 2 Five categories of relations between adverse effects and adverse reactions

Category	Details	Comments
1	The adverse effect leads to appreciable harm	The most common form
2	The adverse effect does not lead to appreciable harm unless amplified by another factor or by combination with another drug-related hazard	Contrasts hazards and harms
3	Appreciable harm occurs without a preceding adverse effect	Paradoxical reactions
4	Dissociation of the adverse effect from the adverse reaction	Typically in drug-drug interactions
5	Syndromes that are combinations of adverse effects and adverse reactions	May be clarified by classifying effects and reactions separately

2.2 The Adverse Effect Does Not Lead to Appreciable Harm

In some cases an adverse effect does not result in harm. For example (Fig. 3), aspirin (acetylsalicylic acid) inhibits platelet aggregation (an effect at the cellular level) by inhibiting cyclo-oxygenase (an effect at the molecular level). This effect is expected to produce benefit, by reducing the risk of myocardial infarction. However, it can also cause an adverse reaction—bleeding—but not unless a modifying (amplifying) circumstance occurs, such as trauma. In this case, if bleeding occurs for any reason, the bleeding will be exacerbated by the adverse effect of the aspirin. Thus, aspirin can amplify the harm caused by trauma, but the adverse (would-be beneficial) effect of aspirin alone does not itself cause an adverse reaction.

The implication of this is that asymptomatic adverse effects that do not result in adverse reactions should not be regarded as harms but rather as hazards. 'Hazard' is the inherent capability of an intervention to cause harm and 'a hazard' is a potential source of harm. Harm from a drug hazard is an unwanted outcome that can take the form of symptomatic hurt (e.g. pain or discomfort) or appreciable cellular or organ damage (e.g. a rash). The terms 'hazard' [9] and 'harm' [10] are well established and do not need further discussion here.

In some cases two hazards combine to produce an adverse reaction, each of which would be harmless on its own. For example, the use of a drug such as primaquine poses a hazard for haemolytic anaemia, by virtue of its oxidative action; however, the adverse reaction does not occur unless there is also a genetic abnormality in erythrocyte redox function, such as glucose-6-phosphate

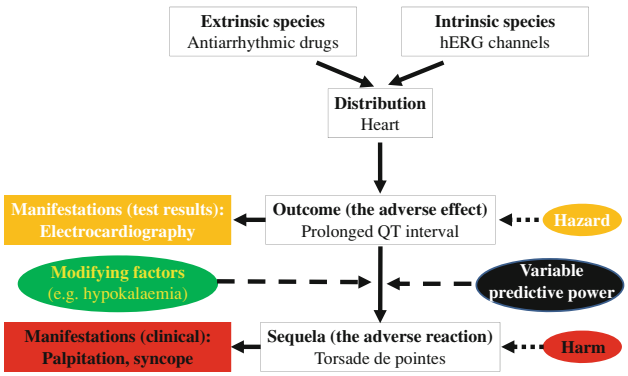

Fig. 2 Torsade de pointes as an adverse reaction to antiarrhythmic drugs; QT interval prolongation is the adverse effect. *hERG* human Ether-à-go-go-Related Gene

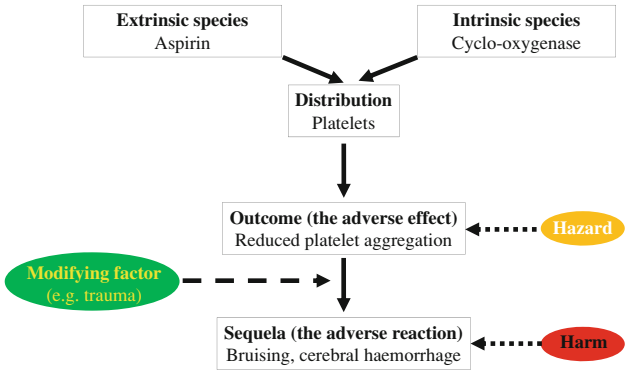

Fig. 3 Bleeding as an adverse reaction to aspirin (acetylsalicylic acid), showing the effect of a modifying factor when the drug is given in a therapeutic dose; impaired platelet aggregation is the adverse effect

dehydrogenase (G6PD) deficiency [11], a modifying or susceptibility factor (Fig. 4).

2.3 Appreciable Harm Occurs Without a Preceding Adverse Effect

It is counterintuitive to suppose that a drug can cause an adverse reaction without having a preceding adverse effect, but that is precisely what happens in certain paradoxical adverse reactions [12, 13]. For example (Fig. 5), in patients with hypertrophic cardiomyopathy the normal action of digoxin in increasing myocardial contractility (an effect at the cellular level), mediated by inhibition of Na^+,K^+-ATPase (an effect at the molecular level), leads not to increased but decreased cardiac output, which is a paradoxical adverse reaction to a normal pharmacological effect [14].

2.4 Dissociation of the Adverse Effect from the Adverse Reaction

In drug-drug interactions, the adverse effect and adverse reaction are dissociated. Each drug is associated with an effect that constitutes a hazard. The hazard posed by the precipitant (perpetrator) drug then causes translation of the hazard posed by the object (victim) drug into an adverse reaction. For example, if erythromycin or clarithromycin inhibits cytochrome P450 (CYP) 2C9 it may reduce the metabolism of warfarin and thereby cause bleeding as an adverse reaction [15]. The twin hazards are the risk of bleeding from warfarin, because of inhibition of vitamin K oxide reductase (VKOR), and inhibition of CYP2C9 by the macrolide. A dose of warfarin that does not normally cause the adverse reaction causes it when the second hazard is superimposed.

Failure of a drug to produce a beneficial outcome has been regarded by some as a drug-related harm. Indeed, failure can legitimately be so regarded if it is due to the effect of a drug interaction. For example (Fig. 6), the benefit of hormonal contraception is avoidance of pregnancy; the hazard is that contraception will fail. However, this can occur because of enzyme induction by rifampicin or carbamazepine [16], which constitutes a superimposed hazard. This extra hazard does not cause an adverse reaction per se, but an adverse sequela occurs nevertheless.

2.5 Syndromes

Some adverse reactions present as syndromes. Such syndromes can consist of mixtures of adverse effects and adverse reactions. An example is shown in Fig. 7. The syndrome known as DRESS (Drug Rash [or Reaction] with Eosinophilia and Systemic Symptoms) is an allergic reaction that has been reported in association with many drugs, but particularly carbamazepine and allopurinol [17]. It consists of a mixture of laboratory abnormalities (eosinophilia, atypical lymphocytes) and adverse reactions (fever, rashes of various types, lymphadenopathy, and liver and other organ damage). Several similar hypersensitivity reactions have been described, such as the anticonvulsant

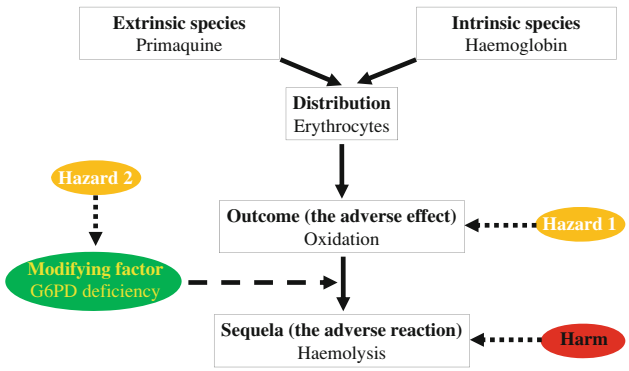

Fig. 4 Haemolysis as an adverse reaction to primaquine; in this case, two hazards interact, producing the adverse reaction. *G6PD* glucose-6-phosphate dehydrogenase

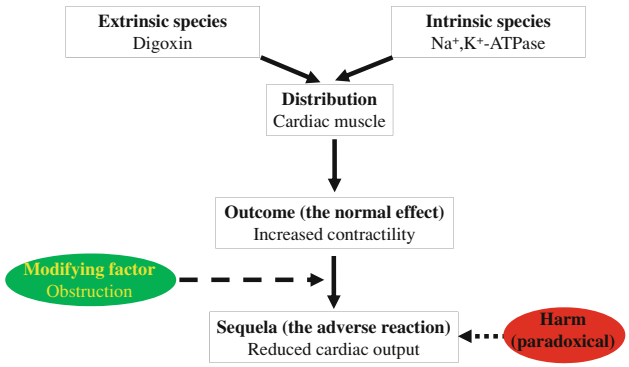

Fig. 5 Reduced cardiac output as a paradoxical adverse reaction to digoxin in patients in whom hypertrophic cardiomyopathy is a modifying factor; in this case the adverse reaction is not preceded by an adverse effect

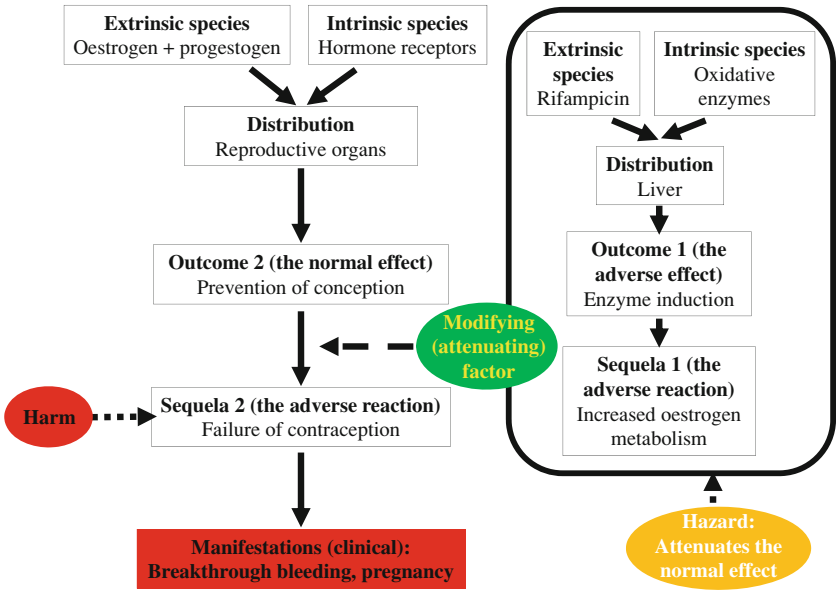

Fig. 6 Failed contraception as a result of an interaction with an enzyme inducer

hypersensitivity syndrome, the drug-induced delayed multiorgan hypersensitivity syndrome, the drug-induced hypersensitivity syndrome, the sulfonamide hypersensitivity syndrome, and the sulfone syndrome. These syndromes may be aetiologically the same as DRESS, but the laboratory abnormalities are not constant features. Classifying the laboratory abnormalities separately from the appreciable harms (the components of the adverse reactions) may help to clarify their taxonomy. This analysis (Fig. 7) also shows the areas in which lack of knowledge needs to be tackled.

3 Defining 'Adverse Effect' and 'Adverse Reaction'

An adverse reaction has been defined in various ways, which have been discussed [2, 18]. In order to define an adverse effect, I have chosen to build on the following definition of an adverse reaction, which specifies the clinical aspects of the reaction, since that is the main feature that distinguishes adverse effects from adverse reactions: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, usually predicting hazard from future administration and warranting prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product". In this definition 'appreciably' means that the reaction is perceptible by the patient or an observer, as either a symptom or some form of noticeable tissue damage.

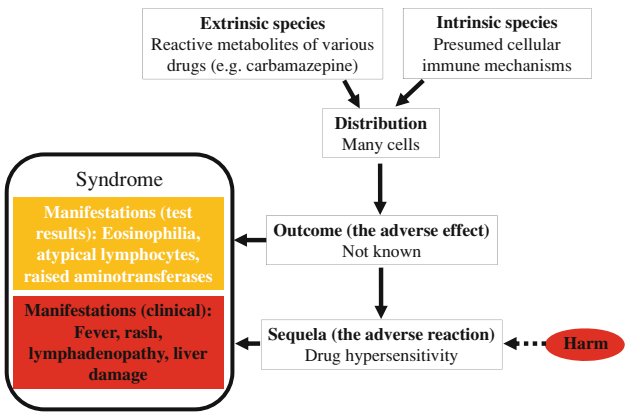

Fig. 7 DRESS, a syndrome that includes both adverse effects and adverse reactions. *DRESS* Drug Rash [or Reaction] with Eosinophilia and Systemic Symptoms

An adverse effect could therefore be defined as "a potentially harmful effect resulting from an intervention related to the use of a medicinal product, which constitutes a hazard and may or may not be associated with a clinically appreciable adverse reaction and/or an abnormal laboratory test or clinical investigation, as a marker of an adverse reaction."

The two keys words here are 'potentially' (for adverse effects) and 'appreciably' (for adverse reactions).

4 Practical Implications: Relevance to Drug Development, Clinical Trials and Pharmacovigilance, Biomarkers, and Monitoring Therapeutic Interventions

This analysis has implications for many areas of drug therapy, including drug development, reporting adverse events in clinical trials, surveillance for adverse drug reactions in pharmacovigilance, the use of biomarkers, and monitoring therapeutic interventions.

4.1 Drug Development

In toxicology and early drug development the concepts of the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL) are familiar [19, 20]. However, these concepts do not distinguish adverse effects from adverse reactions. For example, a compound that produced no observed adverse effect at a given dose might nevertheless produce an adverse reaction (category 3); this would affect the choice of biomarkers. Alternatively, an adverse effect might occur without a consequent adverse reaction (category 2); this would prompt the development of precautionary strategies to avoid converting an adverse effect into an adverse reaction. No/lowest observed adverse reaction levels (NOARLs and LOARLs) should therefore be distinguished from NOAELs and LOAELs.

4.2 Reporting Adverse Events and Detecting Pharmacovigilance Signals

The recording of adverse events in clinical trials would benefit from distinguishing suspected adverse effects from suspected adverse reactions. This could be added as a specific requirement to the CONSORT standards for reporting adverse events in trials [21].

For example, creatine kinase activity rises in patients taking statins, but not all of those so affected develop a myopathy or rhabdomyolysis [22]. Similarly, a positive direct immunoglobulin test occurs in many patients taking drugs such as methyldopa [23], but a frank haemolytic anaemia occurs in only a small minority [24]. Classifying adverse events either as adverse effects without clinical consequences or as adverse reactions would affect the interpretation of pharmacovigilance signals, and investigative and regulatory actions taken as a result.

4.3 Biomarkers and Monitoring Therapeutic Interventions

As illustrated in Figs. 1 and 2, the presence of osteoporosis or prolongation of the QT interval, both adverse effects, need not predict the respective occurrence of fractures or cardiac arrhythmias, both adverse reactions. There are many different patterns of relations between therapeutic interventions and the biomarkers that are used to monitor their effects, whether beneficial or adverse [25], and an analysis of this sort would help in understanding their roles more precisely.

5 Conclusions

All medicines constitute hazards for adverse reactions. An adverse reaction occurs when an adverse effect is translated into an appreciably harmful or unpleasant symptom or organ damage, or sometimes when a susceptibility factor modifies a normal effect. Adverse effects and adverse reactions should be considered separately in the analysis of adverse reactions, and should be separately defined.

Acknowledgments
Funding No outside funding or support was received in the preparation of this manuscript.

Competing interests Jeffrey Aronson has edited textbooks on adverse drug reactions and has provided expert reports and testimony in cases involving adverse drug reactions, but has received no funding from pharmaceutical companies.

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