



## ABCDE SYSTEM (ADVERSE EVENTS OF TYPE A, B, C, D, E)

### HISTORY

Hurwitz and Wade proposed many years ago four categories of adverse events (*Br Med J* 1969; Mar 1 (643):531). The first two mechanisms have been combined under category A and the second two mechanisms under category B.

- Side effect
- Excess effect
- Allergy (hypersensitivity)
- Idiosyncrasy

DeSwarte classified adverse drug reactions (ADRs) into eight categories (*Arch Intern Med* 1986;146:649):

- Overdose
- Side effect
- Secondary, indirect effect
- Interaction
- Intolerance
- Idiosyncrasy (primary toxicity)
- Allergy
- Pseudoallergy (anaphylactoid)

Note that overdose and interaction are risk factors and the indirect or secondary effect is a physiologic consequence. Further information can be found in Meyboom (*PEDS* 1997;16:355) and in Royer (*PEDS* 1997;6:S43).

### TYPE A ADVERSE EVENT

Rawlins and Thompson of Newcastle, Great Britain, have classified adverse events into type A and type B on the basis of the mechanism of action. A type A event is one that is due to an extension of the active pharmacologic properties of the drug (*A* indicates *augmented*). They are also called *predictable* or *anticipated events*. They are generally less severe and more frequent than type B events. This augmented pharmacologic action may occur at the targeted receptors or at other nontargeted receptors producing *lateral effects*, *parallel effects*, or *side effects*. They are usually detected during the clinical trials done before marketing. There are two subclasses:

#### ▶ Exaggerated Desired Effect

*The undesirable exaggeration of a desired pharmacologic effect after a normal dose in a susceptible subject or after a higher than normal dose. This results from the excess stimulation of targeted receptors by the therapeutic agent. Orthostatic hypotension with an antihypertensive, daytime somnolence after a sedative-hypnotic taken for sleep, and hypoglycemic shock after insulin are examples of this phenomenon.*

#### ▶ Undesired Effect

*The appearance of an undesired pharmacologic effect, known as lateral or parallel stimulation, can be seen after a normal dose or a higher than normal dose in a*

susceptible subject; it is due to *the stimulation of untargeted receptors* by the therapeutic agent. Examples include constipation due to morphine, gastrointestinal irritation with nonsteroidal antiinflammatory drugs (NSAIDs), hair loss from chemotherapy, and loss of libido with antidepressants.

#### **TYPE B ADVERSE EVENT**

A type B reaction is one that is not due to an extension of the active pharmacologic properties of the drug; the *B* indicates *bizarre*. They are called *pharmacologically unexpected, unpredictable, or idiosyncratic adverse reactions*.

There are two subclasses:

##### **► Immunologic**

An *allergic or hypersensitivity* reaction occurs as a result of an immunologic mechanism.

A *pseudoallergy or anaphylactoid* reaction is the result of a mechanism involving the release of the same mediators released during an immunologic reaction due to immunoglobulin E (IgE). Such reactions can occur with radiocontrast agents, NSAIDs, for example.

(See ALLERGY, DRUG)

##### **► Idiosyncratic**

The term *idiosyncratic* is often used in a broad sense to designate qualitatively abnormal adverse reactions that occur in a given individual and whose mechanism is not yet understood. These reactions are usually quite rare and in some cases may be due to a genetic or acquired enzyme abnormality with the formation of toxic metabolites. This is also known as *primary toxicity*.

*Congenital enzyme abnormalities* may produce adverse reactions such as the hemolytic anemia due to glucose-6-phosphate dehydrogenase (G6PD) deficiency.

*Acquired enzyme abnormalities* result from a drug effect that produces enzyme inhibition or induction.

Types C, D, and E are not mechanisms but characteristics of their manifestations; they are not referred to frequently in the literature. The letter *C* refers to *continuous, chronic*. Type D refers to *delayed* in appearance, making them difficult to diagnose. Type E refers to *end of use*.

## **ABUSE POTENTIAL (See PHARMACODEPENDENCE)**

## **ACCEPTABILITY (OF AN ADVERSE DRUG REACTION)**

In drug surveillance, an adverse drug reaction (ADR) is deemed acceptable when its frequency and severity are sufficiently compensated for by the frequency and magnitude of the therapeutic benefit of the drug. This is necessarily a value judgment. Similarly to the benefit/risk judgment made in clinical therapeutics for an individual patient, a benefit/risk judgment can be made in pharmacovigilance from a population point of view. When an ADR that is clearly greater than the drug benefit expected occurs (e.g., severe gastrointestinal (GI) bleeding with a mild analgesic), the ADR is referred to as *alarming*. On the other hand, a headache, for example, seen with an acquired immunodeficiency syndrome (AIDS) or cancer medication would be deemed acceptable.

In pharmacotherapy, whenever a product is incorrectly prescribed or used, the benefit expected is considered to be zero for the calculation of the benefit/risk ratio. An example would be the prescription of an antibiotic for a simple cold of viral origin, in which case no ADR would be acceptable since there is no pharmacologic benefit to be expected.

Note also that in the pharmaceutical sciences, the term *acceptability* is used in another sense, namely, that of the quality of the galenic form in regard to ease of administration (timing, mode of administration, volume of the tablet, taste of the suspension, packaging, etc.).

#### **IN CLINICAL PRACTICE**

In the course of pharmacologic therapy, the clinician makes a decision in regard to the acceptability of an ADR and decides whether or not to modify the treatment in a given patient. Here are four examples.

*Before the occurrence of an ADR:* In a patient with newly diagnosed hypertension, the practitioner may hesitate between prescribing a thiazide diuretic and a beta-blocker. However, the presence of asthma in the patient makes the beta-blocker unacceptable. The thiazide is thus chosen in order to prevent the risk of possible bronchospasm with the beta-blocker.

*After the occurrence of an ADR:* A hypertensive patient has an acute episode of gout after having started treatment with a thiazide, which now makes this treatment unacceptable. The clinician substitutes a beta-blocker.

*After the occurrence of an ADR but before the occurrence of the desired beneficial effect:* A patient suffering from prostatitis has been taking an antibiotic. There is no improvement in his symptoms and he is now complaining of daily abdominal discomfort associated with his medication. The prescriber would be more likely to stop the drug, deeming the ADR unacceptable, because the prostatitis was not improving.

*After the occurrence of an ADR and after the occurrence of the desired beneficial effect:* A hypertensive patient tolerates neither thiazides nor beta-blockers. Her blood pressure is well controlled with an angiotensin converting enzyme (ACE) inhibitor, but she has an occasional mild dry cough. After a discussion between the prescriber and the patient, the two agree that the mild cough is acceptable since good pharmacologic control of her blood pressure has been obtained.

#### **ON A POPULATION LEVEL**

Health authorities perform their duties of drug surveillance during the two periods of development of a new product:

*Before marketing authorization:* The authorities responsible for the approval of a new drug must examine the dossier submitted and may refuse to approve the drug if the risks observed during clinical development outweigh the degree of therapeutic innovation, especially when safer alternative therapies are already available.

*After marketing authorization:* After the marketing of a drug, health authorities may take various regulatory measures, ranging from restrictions on the use of the drug to its complete withdrawal from the market. These measures are taken when the risk, first seen in the spontaneous ADR reports, is confirmed by a pharmacovigilance evaluation and when this risk clearly outweighs the expected pharmacologic benefit.

**ABOUT BENEFITS**

Since the comparison of risk to benefit is used during safety investigations and during the selection of regulatory measures, let us review the various types of benefits attainable from a medication:

*Overdose correction:* antidotes, antagonists.

*Diagnostic:* contrast agents, radioisotopes, allergens.

*Cure:* antibiotics, antivirals, gene therapies.

*Prophylaxis:* prevention of cerebrovascular or cardiovascular accidents by hyperlipidemics, antihypertensives, platelet antiaggregants, and antiarrhythmics. In prophylactic pharmacotherapy one must always make the distinction between a *pharmacologic effect*, which serves as an intermediate measure or end point (surrogate marker) used in many clinical trials, and a therapeutic (clinical) benefit, which can often be found only in large, long-term, costly, and relatively rarely performed clinical trials. For instance, the measurement of cholesterol levels in a short-term trial using a new cholesterol lowering agent is a surrogate end point, whereas the measurement of myocardial infarcts, cerebrovascular accidents, and death in a long-term survival study represents the clinical benefit.

*Replacement therapy:* hormones (e.g., insulin), electrolytes (e.g., potassium), metabolites (e.g., glucose), blood products, vitamins (e.g., B<sub>12</sub>), and others.

*Symptomatic treatments:* analgesics, antiemetics, others.

*Treatment of side effect:* use of antihistamines to counter neuroleptically induced ADRs.

**ACCEPTABLE RISK**

The risk of an adverse drug reaction (ADR) becomes acceptable when the expected benefit is greater than the likelihood that the ADR will occur. This is a medical judgment made by the regulatory authorities when approving a new drug, by the physician when prescribing the drug, and by the patient when taking it. It is based on the frequency and severity of the ADR(s), the frequency and magnitude of expected benefit, and the severity of the disease.

**ACCOUNTABILITY**

In the context of pharmacovigilance, *accountability* refers to the responsibility of each person in the development, research, and use of drugs to ensure that they are used in a rational, efficacious, benevolent, and safe manner. There are complex and multiple interdependencies and responsibilities in this chain affecting all parties involved to varying degrees: pharmaceutical companies, legislators, health authorities, medical educators, editors of medical journals, prescribers, sellers, dispensers, and users. The goal of all of the people and organizations involved is to prevent adverse drug reactions (ADRs) due to negligence, imprudence, errors, or “irregularities,” as these ADRs are preventable (see CAUSALITY, Legal).

A textbook covering this area is useful to those in pharmacovigilance and especially those with medicolegal issues (Dukes M, Mildred M, and Swartz B. *Responsibility for drug-induced injury*. Amsterdam: IOS Press, 1998). Another interesting book, written by a layman whose wife suffered an ADR, is Stephen Fried's *Bitter Pills* (New York: Bantam Books, 1998).

## ACKNOWLEDGMENT LETTER

All pharmacovigilance centers (governmental, industrial, or academic) should reply promptly to every person who notifies them of an adverse event. This reply may be a personalized letter but can be a phone call, fax, or e-mail; it should thank the sender for the information, acknowledge its receipt, and ask for further information if needed to clarify the case. If the acknowledgment letter does not produce a response, it is necessary to send a follow-up letter (see this term).

The acknowledgment letter should be sent by a reliable system (such as certified mail) and should contain the following:

- A postal return receipt should be enclosed if sent by mail; this may not be necessary if sent by a private courier that maintains a website capable of tracking all letters and packages sent.
- A statement of appreciation for the report and a request for additional medical information if needed are included. A standardized form may be used (some use a blank CIOMS I form; others use a customized form).
- A postage-prepaid business reply envelope should be included.

Some centers may also send information about similar adverse events already in the data base.

Additional information should be requested when

- The information is insufficient or certain lab tests are needed for validation of the event (e.g., cardiograms, radiograph or scan reports).
- The case represents a particularly important signal.
- The event is very severe medically and that severity may alter the benefit/risk ratio if confirmed.

## ACTIONS (MEASURES) TAKEN

When a signal is felt to be confirmed after a pharmacovigilance investigation, the governmental health authorities and the manufacturer take various measures to reduce inevitable and unacceptable risk in order to make continued use of the product safer.

### REGULATORY MEASURES; REGULATORY ACTIONS TAKEN

Regulatory measures or actions taken represent changes in the status of the drug that are made during or after a pharmacovigilance investigation with the goal of preventing further adverse drug reactions that are judged unacceptable in respect to public health. Such measures can be taken either separately or together by the manufacturer and the health authorities. Actions taken by the manufacturer may be either voluntary or obligatory. In most cases, action is taken only after a signal is confirmed. However, if a new ADR appears to be clearly unacceptable and/or too frequent to allow the risk of waiting for confirmation from a request for intensified adverse effect reporting or from clinical trials, urgent temporary regulatory measures can be taken.

### TRANSMISSION OF INFORMATION: LABEL CHANGES

Changes in medical information are usually included not only in the Product Monograph (labeling) but also in the medical information for the health care professional as well as for the patient (Patient Information Leaflet). Sometimes information is even added to the packaging, for example, by attaching a sticker to the bottle.

If the label changes are significant, they are often referred to as *health authority required* or *regulatory changes* as they are usually governed by the drug laws and regulations of each country, at least in the developed countries. These changes are often the result of a negotiation between the health authorities and the manufacturer (voluntary changes) but may be imposed by the health agency (mandatory or obligatory changes). In many countries, if there is a compelling safety issue, the manufacturer is permitted to make a safety change without prior notification or approval of the authorities if the change is related only to safety and makes the label more restrictive.

These changes produce alterations in the package insert (official labeling) and possibly on the packaging or bottle. These changes can include the following:

- A reduction in the recommended dose
- The removal of one or more indications
- An absolute or relative restriction on the population being treated
- A new contraindication for patients with certain medical conditions or diseases (concomitant morbidity)
- A restriction, contraindication, or warning regarding use with other specific drugs or classes of drugs (drug interaction)
- Use of the product as a secondary or tertiary treatment rather than a primary treatment
- Recommendation of concomitant treatment with another drug to prevent or correct the problem produced by the drug
- Recommendation of periodic lab testing or clinical follow-up (e.g., alanine aminotransferase (ALT) for hepatotoxic products, electrocardiograms (ECGs) for cardiotoxic products)

The changes are sometimes printed in bold letters or presented in a black box to underline the importance of the changes and to note that they are recent additions to the label. Sometimes a “Dear Doctor” (or “Dear Health Care Professional”) letter is sent as well as a press release and a note on the health authority’s website.

#### **LIMITATION OF ACCESS TO THE DRUG**

- Alteration of availability (e.g., changing of its *listedness* or addition of an *annex*): narcotic, controlled drug, limited prescription, “exceptional medication,” temporary use authorization
- Limitation on the prescribers (e.g., reserved only to specialists) for the initial prescription or for renewals
- Limitation on methods of prescription (e.g., no automatic renewals, no telephone prescriptions, limitation of number of tablets dispensed)
- Limitation to hospital dispensation (e.g., new and/or renewals)
- Limitation to place of dispensation: over the counter (OTC) (unrestricted sale in pharmacies) or “behind the counter” (requiring pharmacist consultation) or permit for sale anywhere (e.g., supermarkets): that is, potential change of OTC product to behind the counter or prescription only status
- Obligatory laboratory testing (e.g., negative pregnancy test result before, during, and for some months after stopping of treatment)
- Written justification of the indication by the prescriber
- Informed consent signed by the patient and possibly the prescriber or pharmacist
- Withdrawal of patients under treatment
- Requirement of other measures while taking the drug: (e.g., two methods of contraception for teratogenic medications)

**MODIFICATION OF THE PRODUCT ITSELF****► Change in the Active Ingredient**

Removal or substitution of one of the active ingredients in a combination product

Removal of one of the dosage strengths available (e.g., usually the highest dose though in rare cases it might be the weakest dose if it is judged to be ineffective and only the higher dose has the appropriate benefit/risk ratio); for example, after a pharmacovigilance investigation, removal of the 100-mg dosage form of an antibiotic and retention of the 200-mg form on the market.

**► Change in the Galenic Form**

Change or removal of excipients

Modification of the quantity in the bottle or box

Change in packaging

Change in an accompanying device: for example, when a parenteral product for a chronic infection produces injection site reactions and a different needle is packaged with the product and used for the injection

**► Change in Storage or Preparation**

For example, a refrigerated injectable product that produced pain and burning on injection; marked improvement resulted after the label was changed to indicate that it should be at room temperature before injection.

**WITHDRAWAL FROM MARKET**

- Withdrawal of a particular active ingredient, a specific product, a specific formulation
- Temporary or definitive suspension of sales
- Cessation of manufacture and distribution
- Withdrawal of stocks from the wholesaler, pharmacist, or patient, depending upon the severity of the problem
- Withdrawal (weaning) of the drug from individual patients under medical care

**CHOICE OF COMMUNICATION CHANNELS**

- The labeling in the official monograph (labeling, package insert, summary of product characteristics, etc.)
- The labeling in the packaging documentation (annex)
- The labeling on the sticker of the box or bottle
- A Dear Doctor, Dear Pharmacist, or Dear Health Care Professional letter (soon likely to be e-mail)
- Direct notification of the prescribing physicians by the manufacturer's sales representatives (usually limited to drugs prescribed by limited numbers of specialists)
- A pharmacovigilance bulletin either in writing or on the Internet or in both forms
- An article in a scientific or professional periodical
- A press release to the media and on the Internet
- An alert notification from one health authority or nongovernmental organization (WHO) to another (e.g., WHO Uppsala alert to worldwide health agencies)

- In rare instances, direct use of mass media to alert the general public of a critical safety issue

## ACTIVE INGREDIENT; ACTIVE MOIETY

The principal medicinal ingredient of a pharmaceutical product that is responsible for its pharmacodynamic effects, in contrast to an *excipient* which is (supposedly) inactive but is capable of occasionally producing allergic or toxic adverse drug reactions (ADRs) themselves or of modifying the kinetics of the active ingredient.

The actions of the active ingredient can be modified by confidence that the product has a positive effect (placebo effect) and by a lack of confidence that the product has a negative effect (nocebo effect).

## ADDICTION

Addiction to a pharmaceutical product taken in a “medical” context can be referred to as *pharmacodependence* (see PHARMACODEPENDENCE), to prevent confusion with “street drug” addiction.

## ADMINISTRATION SITE REACTION

One of the nontemporal characteristics of an adverse event (AE) is its location, its “human body topography,” when the reactions occur at the administration site, the transit site, or the concentration site (see TRANSIT SITE REACTION and CONCENTRATION SITE REACTION). Not all “site of administration reactions” are injections (see INJECTION SITE REACTION). Sometimes an adverse drug reaction (ADR) is associated with an error of administration, as in the following example:

*Nonoxynol 9*: This spermicide can be formulated as a vaginal ovule and used as a contraceptive. The first case (index case) of hemorrhagic cystitis due to erroneous insertion into the urethra was published in 1980. Other cases followed. This “site” ADR was obviously not detectable before the commercialization of the product. Only after the first cases were noted could prescribers be informed on how to prevent future cases and how to treat the reaction should it occur. Preventive measures described the precautions needed during insertion of the ovule to prevent urethral penetration (Gottesman, *N Engl J Med* 1980;302:633; Cattolica, *Urology* 1982;20:293; Meyersak, *J Urol* 1993;149:835).

Reactions sometimes stem from nonprescription products. Indeed certain mouthwashes or liquid iron supplements taken without a straw may darken teeth.

## ADVERSE DRUG REACTION (ADR)

The term *adverse drug reaction* is not specifically defined in the Food and Drug Administration (FDA) regulations but FDA has indicated it accepts the ICH definitions.

In the European Medicinal Evaluation Agency (EMA) regulations, the International Conference on Harmonization (ICH) definition is essentially used (CMPM/ICH/377/95):

In the *pre-approval clinical experience* with a new medicinal product or new uses of an old drug, particularly as the therapeutic dose(s) may not be



established: *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.*

The phrase “responses to a medicinal products” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding *marketed medicinal products*, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498(1972) and reads as follows:

*A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiologic function.*

This definition has been agreed to by the International Conference on Harmonization (ICH) (see this term) and has been adopted by many health authorities around the world and the WHO Monitoring Centre (which played a major role in its creation). A copy of the ICH E2B document containing this and other definitions is available ([www.ifpma.org/pdfifpma/e2a.pdf](http://www.ifpma.org/pdfifpma/e2a.pdf)).

In summary, an adverse effect (AE) that is suspected of being related to the drug is an ADR.

## **ADVERSE DRUG REACTION (ADR) CASE REPORT**

Sometimes referred to simply as a *case report* or, to use the ICH E2B terminology, *individual case safety report* (ICSR). This report consists of the details of a published or spontaneously reported adverse event or reaction. Information should include full details of the case to allow proper assessment of causality and seriousness.

## **ADVERSE DRUG REACTIONS ON-LINE INFORMATION TRACKING (ADROIT)**

The software and data base of the Committee on Safety of Medicines (CSM) is the official pharmacovigilance structure of the United Kingdom.

## **ADVERSE EVENT or EXPERIENCE (AE)**

U.S. Food and Drug Administration (FDA) definition (21CFR310.305) is as follows:

*Adverse drug experience:* Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; any adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

The European Medicinal Evaluation Agency (EMA) definition (CMPM/ICH/377/95) is as follows:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note that in some countries, (United States and the European Union) the lack of efficacy of a marketed drug is also, by regulatory definition, an adverse event such that this concept is included in the definition of an AE.

Older definitions exist for this term and, in the past, distinguished between marketed and clinical trial events. Some are mentioned in the following for historical interest.

#### **FOR A MARKETED PRODUCT**

Any clinically undesirable occurrence in a person exposed to a drug whether or not there is a causal link with the drug:

- Even if the drug is not suspected (e.g., a concomitant medication)
- Even if the drug was suspected and exonerated after validation and causality assessment

It is defined by the World Health Organization (WHO) and the International Conference on Harmonization (ICH) as “*any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*” (Edwards, *Drug Saf* 1994;10:93; ICH E2A 1994.)

According to CIOMS I (1990:14) spontaneous alert reports are not supposed to report undesirable events for which causality has not been evaluated. An event becomes a reaction when a physician or other health professional has concluded that there is a “reasonable possibility” or suspicion of a causal link between the undesirable occurrence and the drug.

As soon as there is the slightest suspicion by a clinician, whether or not a formal causality assessment has been done, the *event* becomes a *reaction*. If the causality assessment has ruled out the drug as a cause of the problem, the *reaction* becomes an *event*. Logically then, this case should be removed from the pharmacovigilance data base (whether governmental or corporate). However, in many countries, regulations require that adverse events be kept in the data base as if they were adverse drug reactions (ADRs).

In practice, most pharmaceutical companies do not perform causality assessments on spontaneously reported occurrences from health care practitioners since the very fact that a practitioner thinks enough to report the occurrence at all renders it “possibly related” to the drug and thus a reportable ADR. Many countries (United States, European Union, Canada) consider all spontaneously reported AEs to be, by definition, ADRs.

#### **DURING A CLINICAL TRIAL**

According to ICH, an AE is “*any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment*” (ICH E2A 1994).

According to CIOMS (1;1990:14), “Events are completely and routinely recorded during a study and the rates of these events for different study groups are compared. Only those study events which a physician has judged it reasonable to suspect . . . should be considered as possible subjects of CIOMS reports.”

It is clear that during clinical trials two types of causality analyses are possible:

- Group causality assessment: an unbiased statistical analysis comparing the frequency of AEs between or among the treatment groups