Joining the DoTS: new approach to classifying adverse drug reactions

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A new classification system for adverse drug reactions based on time course and susceptibility as well as dose responsiveness should improve drug development and management of adverse reactions

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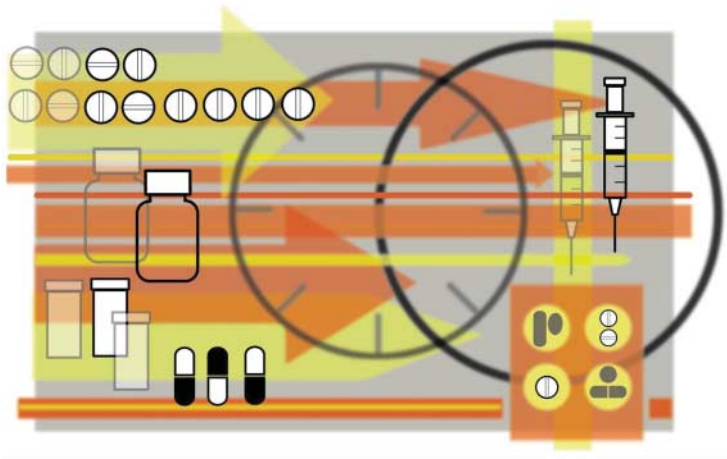
Tables showing how classification of adverse drug reactions has evolved and time related classifaction are available on bmj.com

The pharmacological classification of adverse drug reactions whose causality has been established currently rests on the perceived dose dependence and predictability of the adverse reaction. It is based on a proposal of Rawlins and Thompson, prefigured by others (see table A on bmj.com), to classify adverse drug reactions into two types[1]: type A reactions, dose dependent and predictable from the known pharmacology of the drug; and type B reactions, not dose dependent and unpredictable.[2] This classification is simple; it helps drug regulation because prelicensing studies can reveal type A reactions,[3] and it predicts that dose titration will reduce the risk of some reactions. However, it is sometimes difficult or impossible to assign a reaction to one type. For example, dose dependent (type A) nausea and vomiting due to erythromycin could also be classified as type B because it is not pharmacologically predictable.

Furthermore, other types of adverse reactions are not comfortably classified by the system. For example, osteoporosis from corticosteroids depends not only on dose but also on duration of treatment. And some reactions, such as asthma from β adrenoceptor antagonists, do not occur in all patients. The classification has gradually been extended to other alphabetically labelled types (see table A on bmj.com), including type C (dose and time dependent (chronic) reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy).[4] These modifications have mitigated some of the difficulties of the classification system but have introduced others.

The current classification is defined only by properties of the drug—its known pharmacology and the dose dependence of its effects. However, other criteria should be taken into account in a comprehensive classification, including properties of the reaction (the time course of its appearance and its severity) and properties of the individual (the genetic, pathological, and other biological differences that confer susceptibility). We therefore propose a three dimensional classification system based on dose relatedness, timing, and patient susceptibility (DoTS).



LIANNE PAYNE

Dose relatedness

Traditionally, immunological and certain other adverse drug reactions have been considered not to be dose related. However, effects of drugs involve interactions between chemical entities and are therefore subject to the law of mass action. This implies that all drug effects, beneficial or adverse, are dose related. Examples of immunological reactions that are clearly dose dependent include hay fever in response to high pollen counts[5]; the immunogenic response to hepatitis B vaccine[6]; desensitisation by the use of increasing doses of antigen (for example, cephalosporins)[7]; and type IV hypersensitivity skin reactions.[8]

It is therefore misleading to suggest that type B adverse drug reactions are not dose dependent.[2] In fact, it is clearer to divide adverse drug reactions into reactions that occur at supratherapeutic doses (toxic effects); reactions that occur at standard therapeutic doses (collateral effects); and reactions that occur at subtherapeutic doses in susceptible patients (hypersusceptibility reactions). We use the term collateral effects for reactions that occur at standard therapeutic doses because the term side effects is often colloquially used to refer to all adverse effects. Collateral effects include those that occur due to a different pharmacological effect from the therapeutic action and those that occur through the therapeutic pharmacological effect but in another tissue.

Time relatedness

Many pharmacological effects depend on both the concentration of the drug at the site of action and the time course of its appearance there. For example, a given dose of furosemide (frusemide) induces a greater diuresis when it is infused than when it is given as a bolus.[9] And the toxicity of methotrexate is greater when a low dose is given repeatedly than when the same total amount is given as a single dose.[10]

We distinguish two patterns of time courses of adverse drug reactions, time dependent and time independent (see table B on bmj.com for details of the classification and its implications).

Time independent reactions

Time independent reactions occur at any time during treatment, independent of the duration of the course.

They typically occur either when the concentration ofthe drug at the site of action changes (for example, digoxin toxicity when renal function worsens) or when the pharmacological response is altered without a change in concentration (for example, digoxin toxicity in association with potassium depletion). When such a reaction occurs, its time course may be affected by the kinetics of the drug, but that is not an aspect of its time dependency as defined here.

Time dependent reactions

There are six subtypes of time dependent reactions—rapid, first dose, early, intermediate, late, and delayed.

Rapid reactions occur only when a drug is administered too rapidly—for example, the red man syndrome with vancomycin.[11]

First dose reactions occur after the first dose of a course of treatment and not necessarily thereafter. Examples include hypotension after the first dose of an angiotensin converting enzyme inhibitor[12] and type I hypersensitivity reactions. In type I hypersensitivity reactions the reaction occurs after the first dose of a course, whether or not previous exposure has been recorded; 30% of those who develop anaphylaxis with penicillin have no such record.[13] We regard a previous sensitising exposure as causing a change in susceptibility.

Early reactions occur early in treatment then abate with continuing treatment. These are adverse drug reactions to which patients develop tolerance (such as nitrate induced headache).

Intermediate reactions occur after some delay; however, if a reaction has not occurred after a certain time, there is little or no risk that it will occur later. Examples are hypersensitivity reactions of type II (thrombocytopenia due to quinine), type III (interstitial nephritis with penicillins), and type IV (cutaneous hypersensitivity to antihistamines), and the ampicillin/amoxicillin pseudoallergic rash.[14] Non-allergic reactions of this type include the increased risk of neutropenia with carbimazole and of venous thromboembolism with antipsychotic drugs. 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, after a time the population risk seems to fall.

Late reactions occur rarely or not at all at the beginning of treatment, but the risk increases with continued or repeated exposure. Examples include many of the adverse effects of corticosteroids and tardive dyskinesia with dopamine receptor antagonists. Withdrawal reactions are late reactions that occur when a drug is withdrawn or its dose is reduced after prolonged treatment. They include opiate and benzodiazepine withdrawal syndromes, hypertension after withdrawal of clonidine or methyldopa, and acute myocardial infarction after withdrawal of β blockers.

Delayed reactions are observed some time after exposure, even if the drug is withdrawn before the reaction appears. Examples are carcinogenesis (vaginal adenocarcinoma in women who were exposed to diethylstilbestrol in utero) and teratogenesis (phocomelia due to thalidomide).

Table 1 Sources of altered susceptibility to adverse drug reactions

Source of susceptibility	Examples	Implications
Genetic	Porphyria	Screen for abnormalities; avoid specific drugs
	Succinylcholine sensitivity	
	Malignant hyperthermia	
	CYP isozyme polymorphisms	
Age	Neonates (chloramphenicol[15])	Adjust doses according to age
	Elderly people (hypnotics[16])	
Sex	Alcohol intoxication	Use different doses in men and women
	Mefloquine, neuropsychiatric effects[17]	
	Angiotensin converting enzyme inhibitors, cough	
	Lupus-like syndrome[18]	
Physiology altered	Phenytoin in pregnancy[19]	Alter dose or avoid
Exogenous factors	Drug interactions	Alter dose or avoid co-administration
	Interactions with food (eg grapefruit juice with drugs cleared by CYP3A4[20])	
Disease	Renal insufficiency (eg lithium[21])	Screen for abnormalities; avoid specific drugs; use reduced doses
	Hepatic cirrhosis (eg morphine[22])	

Susceptibility

The risk of an adverse drug reaction differs among members of an exposed population. In some cases the risk of an adverse reaction will be present in susceptible subjects and absent in others. In other cases susceptibility follows a continuous distribution—for example, increasing susceptibility with increasing impairment of renal function. Although reasons for hypersusceptibility may be unknown, several types are recognised. These include genetic variation, age, sex, physiological variation, exogenous factors, and disease (table 1). More than one susceptibility factor can be present.

Using DoTS

To show how the categorical form of the classification works, the box gives examples of three adverse drug reactions that readers of draft versions of this paper have challenged us to classify. Classifying an adverse drug reaction in this way will allow doctors to consider the implications of managing it (see table B on bmj.com).

A more sophisticated probabilistic analysis is also possible, but we shall not discuss it in detail here. It requires an estimate of the probability of an adverse drug reaction at different doses and times after administration, for different degrees of susceptibility. The information can be displayed as a series of three dimensional graphs or equivalent nomograms (figure).

A one dimensional classification system based on time course could meet all the requirements for a useful classification of adverse drug reactions (table 2). For

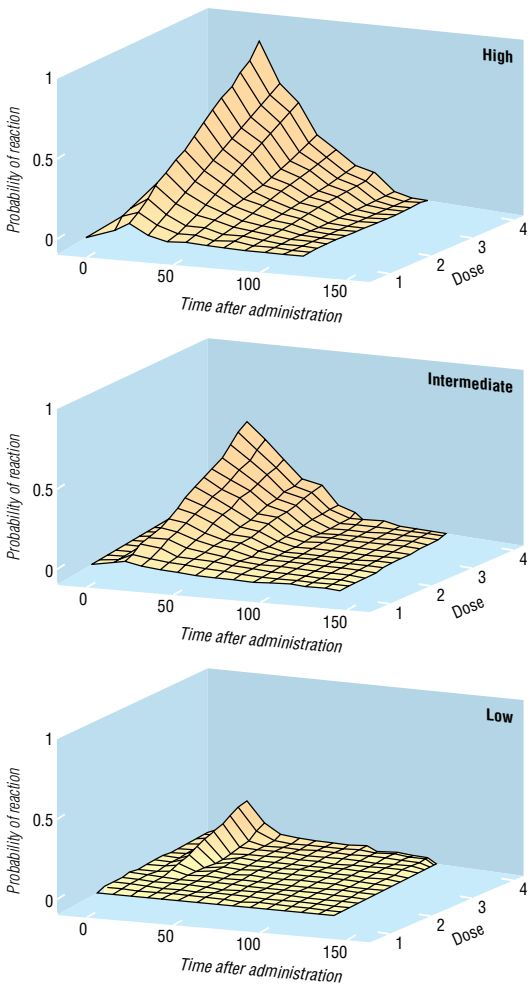
Examples of DoTS (dose-time-susceptibility) classification

- Osteoporosis due to corticosteroids: Do—collateral effect; T—late; S—age, sex.
- Anaphylaxis due to penicillin: Do—hypersusceptilbility; T—first dose; S—not understood; requires previous sensitisation
- Hepatotoxicity due to isoniazid: Do—collateral effect; T—intermediate; S—genetic (drug metabolism), age, exogenous (alcohol), disease (malnutrition)

Table 2 How dose related, time related, and susceptibility related classifications of adverse drug reactions fulfil criteria for satisfactory classification

	Classification		
Criterion	**Dose related**	**Time related**	**Susceptibility related**
Allows classification on basis of clinical features	No; dose dependency is not always clear from clinical observations and dose ranging studies are not always available	Yes; the time course of a reaction can be directly observed in individual cases or populations	Sometimes, depending on type of susceptibility
Give insight into mechanism of reaction	No; only implies the range of doses at which it occurs	Yes; different mechanisms have different time courses	Yes; mechanism and susceptibility are often linked
Avoids assigning a reaction to more than one category	No	Yes	No; an adverse drug reaction may be associated with multiple susceptibility factors
Suggests how to monitor adverse reactions	Yes	Yes	Yes
Suggests population strategies for pharmacovigilance	Yes	Yes; also tells the patient when to be alert for an adverse reaction	Yes (can identify patients at high risk or low risk)
Helps in making decisions on treatment or avoiding adverse reactions	Only some types	Yes	Only some types
Guides drug development and regulation	Yes; can help in defining the therapeutic dosage range	Yes; suggests strategies for monitoring during drug development and after marketing	Yes; defines subgroups at high risk or low risk

example, the time course of a reaction is evident in each patient, so that all reactions can be classified by individual observation, supplemented, if necessary, by observations in the population. The association between halothane and hepatitis was first shown by a careful analysis of the time course of the reaction in individual cases.[23] The time course also helps to distinguish similar adverse drug reactions, such as the two forms of heparin induced thrombocytopenia,[24] the two forms of chloramphenicol induced anaemia,[25] and photoallergic and phototoxic reactions.[26] However, time course alone is an unsatisfactory basis for classification because it ignores important information on dose dependence and individual susceptibility. Our proposal for a three dimensional classification should provide important insights for drug development and regulation, for pharmacovigilance, for monitoring patients, and for the prevention, diagnosis, and treatment of adverse drug reactions.



Graphs showing how probability of adverse drug reaction (y axis) might vary with variations in time after administration (x axis, arbitrary units) and dose (z axis, arbitrary units) in people with high, medium, and low susceptibility having an adverse effect of intermediate type

Summary points

The current classification of adverse drug reactions based on dose response is inadequate

The time course of the reaction and the susceptibility of the patient also need to be taken into account

A three dimensional approach to adverse drug reactions is proposed based on dose, time, and susceptibility (DoTS)

This approach would improve drug development and patient care

We thank those who have commented on these ideas while we were developing them, in particular Stephen Evans and Ralph Edwards.

Contributors and sources: The authors are clinical pharmacologists with long experience of caring for patients with, and collating information on, adverse drug reactions. The ideas expressed in this paper have evolved through frequent discussions of the classification problems and by studying the nature of reported examples, as reviewed in the *International Encyclopedia of Adverse Drug Reactions*, *Meyler's Side Effects of Drugs*, and its annual update volumes (*Side Effects of Drugs Annuals*), both edited by JKA, and *The Textbook of Adverse Drug Reactions*, co-edited by REF.

Competing interests: JKA is vice chairman of the Medicines Commission and chairman of the joint (Committee on Safety of Medicines and Medicines Commission) working group on the prescribing, supply, and administration of medicines. REF is chair of the Medicines and Healthcare Products Regulatory Agency (MHRA) working group on electronic reporting of adverse drug reactions and a member of the Committee on Safety of Medicines expert advisory panel. However, the views expressed here should not necessarily be taken to reflect the views of the Medicines Commission, the CSM, or the MHRA.

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Endpiece

Edinburgh poverty 1840

Deficient nourishment, want of employment, and privations of all kinds, and the consequent mental depression …

Famine, destitution, and pestilence …

Female labourers live in a condition to which that of most domestic animals is a luxury.

Craig WS. *History of the royal college of physicians of Edinburgh*. Oxford: Blackwell, 1976:18-22,43

Jeremy Hugh Baron,
honorary professorial lecturer,
Mount Sinai School of Medicine,
New York

A memorable patient

Cold comfort

In 1968 I was doing my first job as a preregistration surgical house officer in a small district general hospital. The consultant general surgeon was competent, benign, and compassionate, the nurses were good, and we all thought that the whole team functioned rather well, apart from the usual 100 hour working week.

A young woman with inoperable widespread ovarian cancer appeared in one the beds. I was not sure why she had been admitted; I think she probably had a transfusion, and there may have been a problem with her home care. She was skeletally thin with that translucent quality associated with terminal illness. The nurses fed and bathed her and reported that she was not in pain, so I thought that everything was as good as it could be. On ward rounds we stopped at her bed and exchanged pleasantries. She sank into a torpor. We walked past her bed glancing at the pitifully small fetal shape under the bedclothes, with a wisp of hair showing on her pillow. It seemed like an intrusion to disturb her. She died, to everyone's relief, and her bed was then occupied by an altogether more satisfying patient, someone who stood a fair chance of going home better than when she had come in.

Some weeks later, the consultant produced an audio cassette tape for one of our regular clinical meetings. It was about a new institution called "Saint Christopher's Hospice" that had been started the year before. The voice on the tape was, I am sure, no less than the now famous Cicely Saunders. As we listened, I became suffused with shame and guilt. All of us were thinking of the wretched patient we had watched die. There were so many things that we could have done but had failed to do, and there were so many things that we had done but ought not. One of the most notable was the way in which we had walked past the end of her bed without any contact. We left the room in silence, avoiding eye contact. We had cared for the patient's body but neglected her soul.

It was a signal moment that I have recalled so often down the years. Of course, in those days there was no teaching in care of the dying patient, so I took small comfort in my ignorance, but deep down I had to acknowledge that failure of the system does not excuse individual responsibility. Everyone should have salutary experiences, preferably at the start of a career. Mine was worth an awful lot of CPD/CME points.

Mark Griffiths *professor of oral medicine, Eastman Dental Institute, University College London*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. Please submit the article on http://submit.bmj.com Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.