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EIDOS

A Mechanistic Classification of Adverse Drug Effects

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Abstract

The mechanisms of adverse drug effects have not been adequately classified. Here, we propose a comprehensive mechanistic classification of adverse drug effects that considers five elements: the Extrinsic chemical species (E) that initiates the effect; the Intrinsic chemical species (I) that it affects; the Distribution (D) of these species in the body; the (physiological or pathological) Outcome (O); and the Sequela (S), which is the adverse effect. This classification, which we have called EIDOS, describes the mechanism by which an adverse effect occurs; it complements the DoTS classification of adverse effects (based on clinical pharmacology), which takes into account Dose responsiveness, Time course, and Susceptibility factors. Together, these two classification systems, mechanistic and clinical, comprehensively delineate all the important aspects of adverse drug reactions; they should contribute to areas such as drug development and regulation, pharmacovigilance, monitoring therapy, and the prevention, diagnosis, and treatment of adverse drug effects.

An elderly woman falls and fractures her femur. There are many ways in which drugs could have contributed to the fall:

- postural hypotension (nifedipine);
- complete heart block (atenolol) or a cardiac arrhythmia (terfenadine), causing syncope;
- ataxia (carbamazepine);
- parkinsonism with a festinant gait (prochlorperazine);
- a peripheral sensory neuropathy (isoniazid);
- proximal muscle weakness (levothyroxine sodium);
- visual impairment (the anticholinergic effects of oxybutynin);
- a slippery bath (emulsifying ointment used to rehydrate dry skin).

In addition, glucocorticoid-induced osteoporosis would increase the risk of a fractured femur after a fall. Each of these adverse effects is produced by a different mechanism.

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’.[1] Here we use the term ‘drug’ as shorthand to refer to the whole medicinal product, although the species that produces the adverse effect may not be the drug itself. The terms ‘adverse reaction’ and ‘adverse effect’ refer to the same phenomenon, but an adverse effect is seen from the point of view of the drug, while an adverse reaction is seen from the point of view of the patient; the drug causes an effect, while the patient experiences a reaction.

Previous discussion of the general mechanistic aspects of adverse drug effects has been incomplete and has concentrated on susceptibility factors,[2,3] pharmacological/immunological mechanisms, or the actions of metabolites,[4] or has been limited to biological agents.[5] There has been no systematic attempt to classify these mechanisms.

Here we propose a comprehensive mechanistic classification of adverse drug effects. Many adverse drug effects are described as ‘avoidable’ or ‘preventable’, including those that arise from prescribing faults, prescription errors, and other types of medication errors.[6] We do not discuss the systems factors or behavioural factors that permit such adverse effects to occur. We consider only the biological mechanisms that give rise to adverse drug effects.

1. Classifying Adverse Drug Effects Mechanistically

We call this mechanistic classification system EIDOS (table I, figures 1–3), which is a mnemonic for its components, and also reflects the Greek word eidos, which means, among other things, formal cause:

E = the Extrinsic chemical species that initiates the effect;
I = the Intrinsic chemical species that it affects;
D = the Distribution in the body of these species;
O = the (physiological or pathological) Outcome;
S = the Sequela (the adverse effect).

This mechanistic classification complements the clinical pharmacological classification that we have previously described – DoTS (figure 3).[7] DoTS classifies on the grounds of (i) Dose responsiveness, detailing the relation between the dose-response curve for benefit and the dose-response curve(s) for harm and thus distinguishing among hypersusceptibility, collateral, and toxic reactions; (ii) Time course, which can be rapid, first-dose, early, intermediate, late, or delayed; and (iii) the presence or absence of factors that alter the Susceptibility to the adverse effect.

EIDOS describes aspects of the mechanism by which the adverse effect arises, while the DoTS classification describes the clinical features of the adverse effect once it has occurred.

1.1 The Extrinsic Species Involved in the Adverse Effect

Adverse drug effects result from the introduction into the body of an extrinsic chemical species (E) in a medicinal product, or a species derived from it (E′), e.g. by metabolism. Different extrinsic species can be involved in adverse effects:

- *The drug molecule itself*. For example, indometacin inhibits renal prostaglandin synthesis and can cause renal impairment as a result.[8]
- *An excipient*. For example, polyoxyl 35 castor oil (Cremophor EL), which is used to make aqueous solutions of lipid-soluble drugs, such as ciclosporin (Sandimmun®), can cause non-IgE-mediated anaphylactic reactions.[9]
- *A contaminant*, such as 1,1′-ethylidenebis (L-tryptophan), a by-product of manufacture present in certain batches, produced eosinophilia-myalgia syndrome in patients treated with L-tryptophan.[10]
- *An adulterant*, such as lead or arsenic in herbal remedies,[11] or over-sulfated chondroitin sulfate deliberately introduced into batches of heparin.[12]
- *A degradation product* (before introduction into the body), such as the degradation products in outdated tetracycline that led to renal tubular damage.[13]
- *A derivative* (E′) of one of the above, particularly a metabolite of the parent compound,[14,15] e.g. the hepatotoxin hydrazine, a metabolite of isoniazid.[16]

Identifying the type of extrinsic species responsible for an adverse effect has practical implications: if it is the parent drug, the drug may have to be avoided or its dosage reduced; an excipient, contaminant, or adulterant can be removed from the formulation; when breakdown products of tetracycline were identified as causing Fanconi’s syndrome, the limited shelf life of tetracycline was recognized; the identification of acrolein as a metabolite of cyclophosphamide led to the introduction of mesna to prevent haemorrhagic cystitis.

Table I. The EIDOS mechanistic classification of adverse drug effects

Feature		Varieties	Examples
E.	Extrinsic species	The parent compound	Insulin
		An excipient	Polyoxyl 35 castor oil
		A contaminant	1,1′-ethylidenebis (L-tryptophan)
		An adulterant	Lead in herbal medicines
		A degradation product formed before the drug enters the body	Outdated tetracycline
		A derivative of any of these (e.g. a metabolite)	Acrolein (from cyclophosphamide)
I.	The intrinsic species and the nature of its interaction with the extrinsic species:		
	(a) molecular	Nucleic acids	
		DNA	Melphalan
		RNA	Mitoxantrone
		Enzymes	
		reversible effect	Edrophonium
		irreversible effect	Malathion
		Receptors	
		reversible effect	Prazosin
		irreversible effect	Phenoxybenzamine
		Ion channels/transporters	Calcium channel antagonists; digoxin and Na^+/K^+-ATPase
		Other proteins	
		immunological proteins	Penicilloyl residue hapten
		tissue proteins	N-acetyl-*p*-benzoquinone-imine (paracetamol [acetaminophen])
	(b) extracellular	Water Hydrogen ions (pH) Other ions	Glucose 5% Sodium bicarbonate Sodium ticarcillin
	(c) physical or physicochemical	Direct tissue damage Altered physicochemical nature of the extrinsic species	Intrathecal vincristine Sulindac precipitation
D.	Distribution	Where in the body the extrinsic and intrinsic species occur (affected by pharmacokinetics)	Antihistamines cause drowsiness only if they affect histamine H_1 receptors in the brain
O.	Outcome (physiological or pathological change)	See table II	
S.	Sequela	The adverse effect (Dose, Time, Susceptibility [DoTS] classification)[1]	

1.2 The Intrinsic Species and the Form of its Interaction with the Extrinsic Species

There are three types of interaction between an extrinsic chemical species and an intrinsic chemical species (a tissue or fluid in the body) that can result in an adverse effect.

1. *Molecular interactions*: Most interactions between the extrinsic species (E or E′) and the intrinsic species (I) are molecular, i.e. E (or E′) will bind with some affinity to one or more intrinsic molecules of the types listed in section 1.2.1).
2. *Alterations in the extracellular environment*: Some adverse effects result from alterations in the

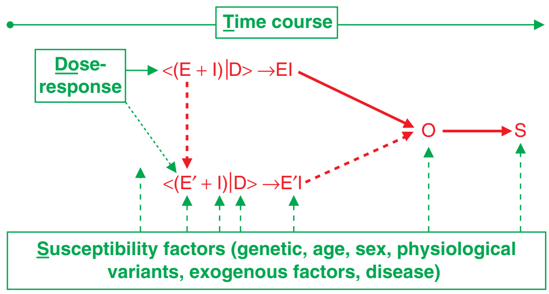

Fig. 1. The relationship between the EIDOS and DoTS classifications. EIDOS classifies the mechanism by which a medicine causes an adverse reaction. E (or E′) is the extrinsic species (or metabolite) that interacts with I, an intrinsic species, provided D, the distribution, brings the two into contact. EI (or E′I) engenders O, an outcome, whose sequela, S, is observed as the adverse effect. Clinically, S is seen at some characteristic time after the administration of a dose (or many doses) of the medicine, as described by the time course, T. The probability that an adverse reaction will occur depends on Do, the relationship between the dose-response curve of the beneficial effect and the dose-response curve of the adverse effect, and on several possible susceptibility factors, S, that can operate anywhere along the causal pathway. The EIDOS and DoTS systems are outlined in figure 3.

composition of the extracellular fluid, e.g. by dilution, alteration of hydrogen ions, or alterations in the concentrations of solutes, such as sodium or potassium ions.

3. *Physical or physicochemical effects*: Adverse effects sometimes result from physical or physicochemical effects, such as direct tissue damage or precipitation of a drug (e.g. within the renal tubules, in the bile, or in the stomach).[17]

1.2.1 Molecular Interactions

The intrinsic molecules that can be involved in interactions with extrinsic molecules include:

- *Nucleic acids*: Covalent adducts between cellular DNA and alkylating agents, such as melphalan,[18] probably explain the increased risk of leukaemia in patients treated with these drugs.
- *Enzymes*: Most drug action involving enzymes is via enzyme inhibition. Some drug interactions involve induction.
  (a) *Reversible effects*: The peptidase that metabolizes angiotensin I to angiotensin II, angiotensin-converting enzyme (ACE), also metabolizes bradykinin; ACE inhibitors therefore inhibit the breakdown of bradykinin, whose increased concentration probably explains the adverse effects of angioedema and cough.[19] Drugs that inhibit or induce enzymes related to drug metabolism are also associated with adverse effects through drug interactions, and these are included as susceptibility factors in the DoTS classification.[1]
  (b) *Irreversible effects*: Inhibition of platelet cyclo-oxygenase by aspirin (acetylsalicylic acid),[20] with a consequent tendency to haemorrhage that persists for several days after the end of treatment, is irreversible.
- *Receptors*: Pharmacological receptors (including neurotransmitter, hormone, and cytokine receptors) are the main targets for the actions of drugs. Adverse effects can result from altered receptor action, in the target organ or elsewhere, either by a direct effect of the drug on the receptor (e.g. agonists and antagonists) or by indirect effects (e.g. neurotransmitter releasers or inhibitors of neurotransmitter reuptake or metabolism). For example, fenfluramine increases the release of serotonin, which stimulates the serotonin 5-HT_{2B} receptor, activating

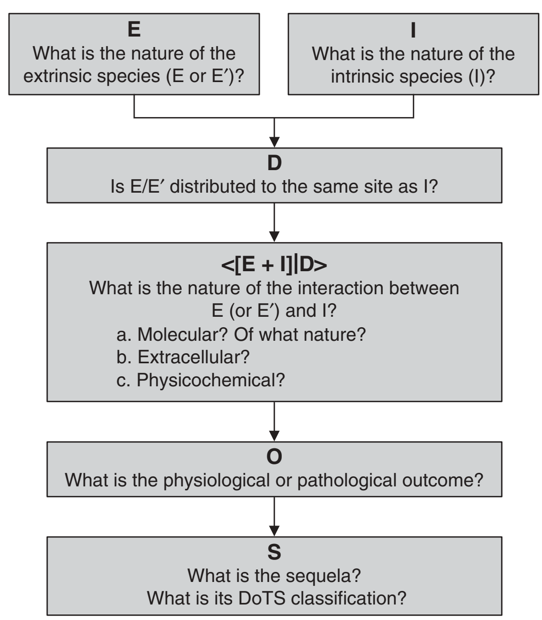

Fig. 2. The questions to be asked at each stage of the EIDOS classification process. **DoTS** = Dose relationship, Time course, Susceptibility.[1]

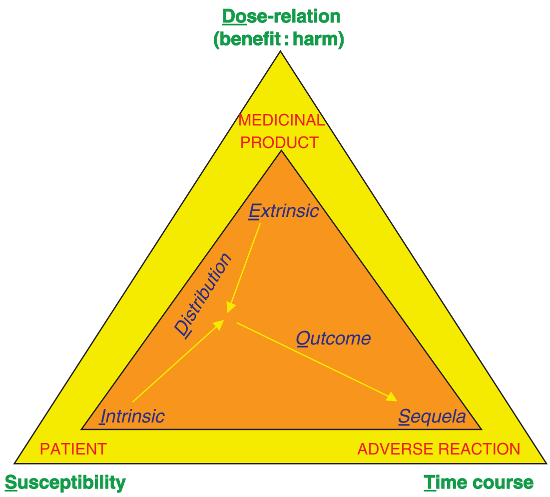

Fig. 3. Two complementary forms of classification of adverse drug reactions. An adverse reaction occurs when a medicinal product is administered to a patient (red upper case text). Adverse reactions can be classified mechanistically (EIDOS; blue italicized text) by noting that the extrinsic (drug) species, when co-distributed with one or more intrinsic (patient) species, has a pharmacological or other effect (the outcome), producing the adverse effect (the sequela). It can be further classified using the DoTS clinical classification (green bolded text), which defines the important aspects of the drug (the relationship between the dose-response curves for benefits and harms, the patient (susceptibility factors), and the reaction (its time course).

kinases that stimulate cell growth in pulmonary valve tissue, causing pulmonary valve lesions.[21] Irreversible receptor inactivation by covalent interaction, e.g. inhibition of α-adrenoceptors by phenoxybenzamine,[22] can lead to collateral adverse effects.

- *Ion channels/transporters*: Inhibition of potassium channels in the distal convoluted tubule of the kidney by triamterene causes hyperkalaemia.[23] Excess inhibition of the $Na^+/K^+/2Cl^-$ co-transporter by loop diuretics in the loop of Henle in the kidney causes hyponatraemia and dehydration.[24]
- *Other proteins*:
  (a) *Immunological proteins*: Immunological effects of all the four types classified by Gell and Coombs[25] can result from interactions between large extrinsic molecules (e.g. peptides and proteins) and intrinsic proteins or cells, from direct effects on components of the immune pathway, or by formation of immunogenic adducts, as exemplified by the haptens formed between the penicilloyl moiety of β-lactam antibacterial agents and intrinsic proteins.[26] Such effects include the interaction between penicillins and IgE, causing anaphylaxis in sensitized individuals, or between proteins in horse serum and IgG, leading to serum sickness in those treated with horse-derived snake anti-venoms.[27]
  (b) *Tissue proteins*: Direct damage to structural proteins can cause functional derangement, as happens when the metabolite N-acetyl-*p*-benzoquinone-imine (NAPQI) binds covalently to sulfhydryl-containing hepatic and renal proteins after paracetamol (acetaminophen) poisoning.[28]

1.2.2 Alteration of the Extracellular Environment

The extracellular environment can change as a consequence of molecular interactions of the types mentioned above, as happens, for example, when chlorpropamide acts on vasopressin receptors.[29] However, there can be direct or non-specific effects on the components of the extracellular environment. These can affect water, hydrogen ions (pH), and other ions.

- *Water:* Crystalloids, such as 5% glucose, can cause water intoxication directly; absorption of glycine solution during transurethral resection of the prostate gland[30] can have important, albeit transient, effects on cardiovascular and neurological function.
- *pH*: Changes in hydrogen ion concentration can lead to important local or systemic adverse effects. Large-volume infusions of solutions (such as sodium chloride 0.9%) that contain strong anions can cause metabolic acidosis.[31]
- *Other ions*: High concentrations of cations, such as sodium, can result directly from the use of antibacterial drugs made up as salts, such as sodium ticarcillin.[32]

1.2.3 Physical or Physicochemical Interactions

Examples of adverse effects that result from physical or physiochemical effects include renal calculi due to precipitation of triamterene in the renal tract and gallstones due to precipitation of sulindac in the biliary tract.[15] Corrosives, for example phenol used for nerve ablation, can cause non-specific tissue damage.[33]

1.3 Distribution

The extrinsic (E [or E′]) and intrinsic (I) species will interact only when they are both found in the same place. Thus, the pharmacokinetics of the extrinsic species can affect the occurrence of adverse effects. For example, histamine H_1 receptor antagonists (antihistamines), such as chlorphenamine, that cross the blood-brain barrier can act on CNS histamine receptors and cause drowsiness. Newer antihistamines, such as cetirizine, do not generally cross the blood-brain barrier in significant amounts and do not reach CNS H_1 receptors; they therefore do not cause drowsiness.[34]

1.4 Outcome of the Interaction

Interactions between extrinsic and intrinsic species in the production of an adverse effect can result in physiological or pathological changes. Examples of these are listed in table II, using a pathological classification based on that described in *Robbins & Cotran Pathologic Basis of Disease*.[46] Some adverse effects arise through a combination of mechanisms.

1.5 Sequelae

The sequelae of the pathological changes induced by a drug constitute the final step in this

Table II. Examples of physiological and pathological changes in adverse drug reactions (some categories can be broken down further)

Type of change	Examples
Physiological changes	
Increased actions	Hypertension (monoamine oxidase inhibitors); clotting (tranexamic acid)
Decreased actions	Bradycardia (β-adrenoceptor antagonists); QT interval prolongation (antiarrhythmic drugs)
Cellular adaptations	
Atrophy	Lipoatrophy (subcutaneous insulin); glucocorticoid-induced myopathy
Hypertrophy	Gynaecomastia (spironolactone)
Hyperplasia	Pulmonary fibrosis (busulfan); retroperitoneal fibrosis (methysergide)
Metaplasia	Lacrimal canalicular squamous metaplasia (fluorouracil)[35]
Neoplasia[36]	
benign	Hepatoma (anabolic steroids)[37]
malignant	
hormonal	Vaginal adenocarcinoma (diethylstilbestrol)[38]
genotoxic	Transitional cell carcinoma of bladder (cyclophosphamide)[39]
immune suppression	Lymphoproliferative tumours (ciclosporin)[40]
Altered cell function	IgE-mediated mast cell degranulation (class I immunological reactions)
Cell damage	
Acute reversible damage	
chemical damage	Periodontitis (local application of methylenedioxymetamfetamine [MDMA, ‘ecstasy’])[41]
immunological reactions	Class III immunological reactions
Irreversible injury	
cell lysis	Class II immunological reactions
necrosis	Class IV immunological reactions; hepatotoxicity (paracetamol, after apoptosis)
apoptosis	Liver damage (troglitazone)[42]
Intracellular accumulations	
Calcification	Milk-alkali syndrome[43]
Drug deposition[15]	Crystal-storing histiocytosis (clofazimine)[44] Skin pigmentation (amiodarone)[45]

Table III. Examples of the classification of adverse effects using the EIDOS and DoTS systems

Classification	Examples		
	a *fall due to nifedipine*	*a fall due to prochlorperazine*	*osteoporosis due to a glucocorticoid*
EIDOS			
Extrinsic species	The parent drug	The parent drug and metabolites	The parent drug
Intrinsic species	Calcium channel antagonists	Dopamine receptors	Calcium homeostasis; osteoblasts
Distribution	Vascular smooth muscle	Extrapyramidal tracts	Sites of calcium transport; bone
Outcome	Physiological: vasodilatation	Physiological: parkinsonism	Atrophy: osteoporosis
Sequelae	Fall and fracture	Fall and fracture	Fracture
DoTS			
Dose relation	Toxic	Collateral	Collateral
Time course	Time independent	Early persistent	Late
Susceptibility factors	Old age, other drugs	Old age	Postmenopausal women

classification and describe the clinically recognizable adverse drug reaction. There may be more than one sequela of an adverse drug effect; in our introductory case, a drug-related fall led to a fracture.

Sequelae can be classified using the DoTS system, thus completing the combined mechanistic and clinical classification, as the examples in table III show, drawing again on our introductory case.

Adverse drug interactions can also be accommodated in this classification. An adverse effect that arises as a result of an interaction can be classified mechanistically by EIDOS in the same way as any other adverse effect. The fact that it is due to an interaction is dealt with by the susceptibility part of DoTS; the interacting drug constitutes the susceptibility factor. An example is given in table III (see the column relating to nifedipine).

2. Discussion

The DoTS classification is a clinical classification of the observed features of adverse drug reactions. It could be used, for example, in pharmacovigilance planning[47] and in developing regulatory strategies for dealing with new adverse drug reactions after a drug has been given marketing authorization.[48] EIDOS, which considers the mechanisms of adverse drug effects, extends the idea of rational classification to encompass non-clinical information. When relevant data are absent, EIDOS provides a framework for assembling them. It cannot, of course, guide decisions in the absence of such data.

3. Conclusion

We believe that the DoTS and EIDOS classification schemes, which comprehensively delineate all the important aspects of adverse drug reactions, could together contribute to areas such as drug development and regulation, pharmacovigilance, monitoring therapy, and the prevention, diagnosis and treatment of adverse drug reactions.

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