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Special reviews in SEDA-35

Cumulative indexes of special reviews, Annuals 4–34

Special reviews were introduced into the *Side Effects of Drugs* volumes in Annual 4. The following two indexes refer to the medications covered in these reviews and the systems involved. The format 34.322 refers to SEDA-34, p. 322.

1. Index of medications in special reviews

2. Index of adverse effects and adverse reactions in special reviews

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Mechanistic and clinical descriptions of adverse drug reactions

Adverse drug reactions are described in SEDA using two complementary systems, EIDOS and DoTS (1–3). These two systems are illustrated in Figures 1 and 2 and general templates for describing reactions in this way are shown in Figures 3–5. Examples of their use have been discussed elsewhere (4–8).

1. EIDOS

The EIDOS mechanistic description of adverse drug reactions (3) has five elements:

- the **Extrinsic** species that initiates the reaction (Table 1);
- the **Intrinsic** species that it affects;
- the **Distribution** of these species in the body;
- the (physiological or pathological) **Outcome** (Table 2), which is the adverse effect;
- the **Sequela**, which is the adverse reaction.

Extrinsic species This can be the parent compound, an excipient, a contaminant or adulterant, a degradation product, or a derivative of any of these (e.g. a metabolite) (for examples see Table 1).
Intrinsic species This is usually the endogenous molecule with which the extrinsic species interacts; this can be a nucleic acid, an enzyme, a receptor, an ion channel or transporter, or some other protein.
Distribution A drug will not produce an adverse effect if it is not distributed to the same site as the target species that mediates the adverse effect. Thus, the pharmacokinetics of the extrinsic species can affect the occurrence of adverse reactions.
Outcome Interactions between extrinsic and intrinsic species in the production of an adverse effect can result in physiological or pathological changes (for examples see Table 2). Physiological changes can involve either increased actions (e.g. clotting due to tranexamic acid) or decreased actions (e.g. bradycardia due to beta-adrenoceptor antagonists). Pathological changes can involve cellular adaptations (atrophy, hypertrophy, hyperplasia, metaplasia, and neoplasia), altered cell function (e.g. mast cell degranulation in IgE-mediated anaphylactic reactions), or cell damage (e.g. cell lysis, necrosis, or apoptosis).
Sequela The sequela of the changes induced by a drug describes the clinically recognizable adverse drug reaction, of which there may be more than one. Sequelae can be classified using the DoTS system.

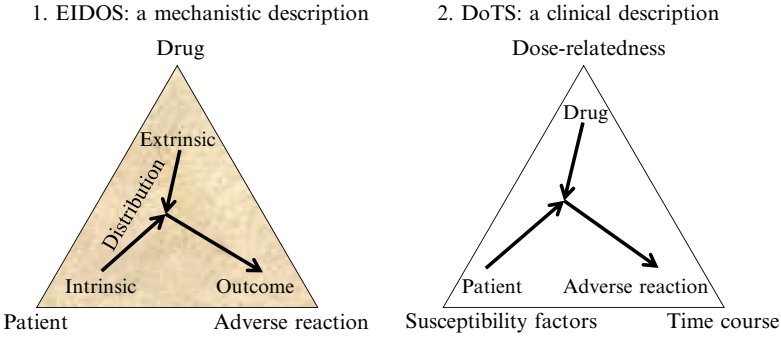

Figure 1 Describing adverse drug reactions—two complementary systems. Note that the triad of drug–patient–adverse reaction appears outside the triangle in EIDOS and inside the triangle in DoTS, leading to Figure 2.

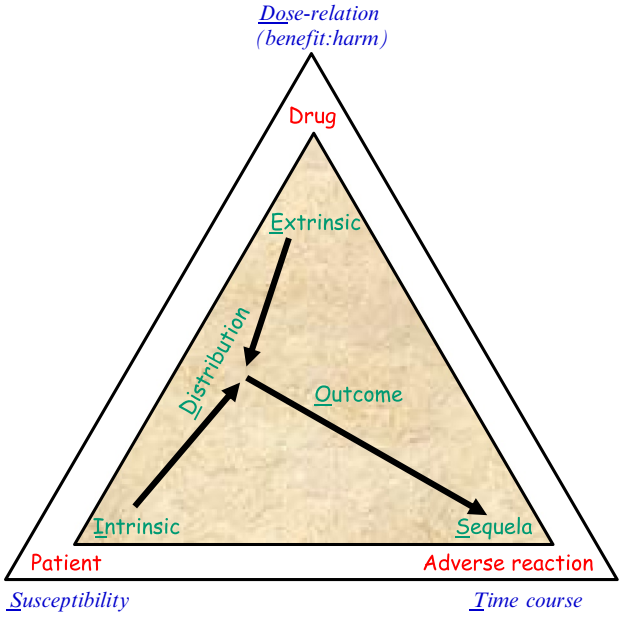

Figure 2 How the EIDOS and DoTS systems relate to each other. Here the two triangles in Figure 1 are superimposed, to show the relation between the two systems. An adverse reaction occurs when a drug is given to a patient (Gothic letters). Adverse reactions can be classified mechanistically (EIDOS; sans-serif letters) by noting that when the Extrinsic (drug) species and an Intrinsic (patient) species, are co-Distributed, a pharmacological or other effect (the Outcome) results in the adverse reaction (the Sequela). The adverse reaction can be further classified (DoTS; serif italics) by considering its three main features—its Dose-relatedness, its Time-course, and individual Susceptibility.

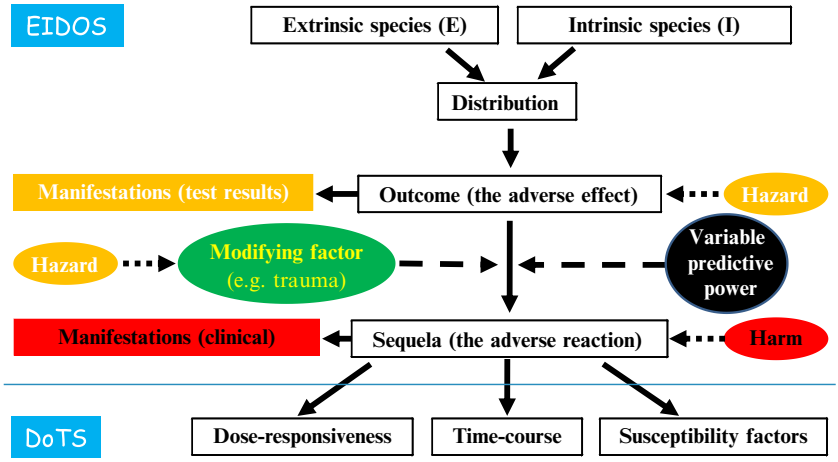

Figure 3 A general form of the EIDOS and DoTS template for describing an adverse effect or an adverse reaction.

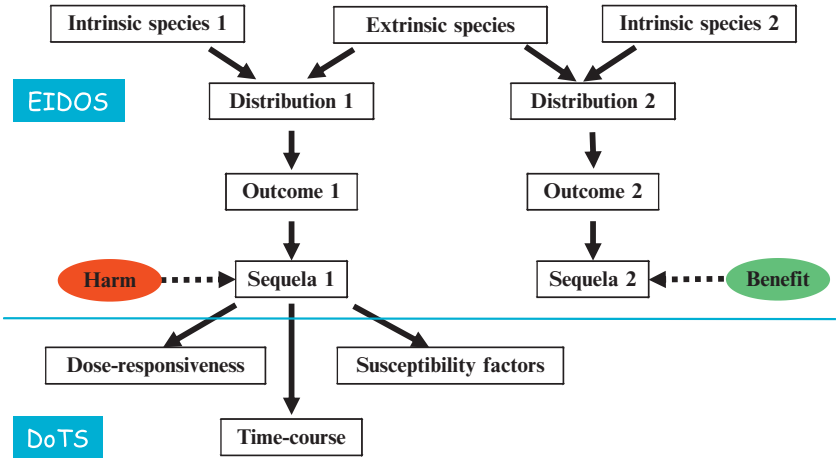

Figure 4 A general form of the EIDOS and DoTS template for describing two mechanisms of an adverse reaction or (illustrated here) the balance of benefit to harm, each mediated by a different mechanism.

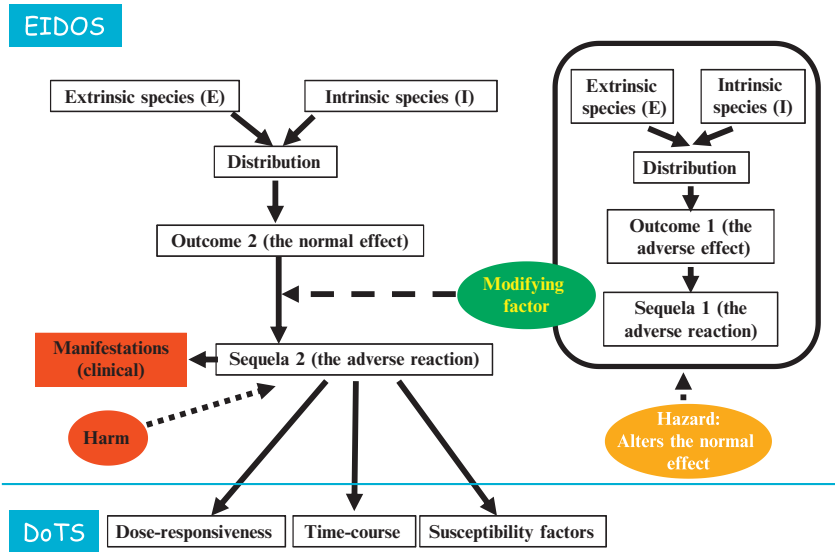

Figure 5 A general form of the EIDOS and DoTS template for describing an adverse drug interaction.

Table 1 *The EIDOS mechanistic description of adverse drug effects and reactions*

Feature		Varieties	Examples
E.	Extrinsic species	1. The parent compound	Insulin
		2. An excipient	Polyoxyl 35 castor oil
		3. A contaminant	1,1-ethylidenebis [L-tryptophan]
		4. An adulterant	Lead in herbal medicines
		5. A degradation product formed before the drug enters the body	Outdated tetracycline
		6. 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	1. Nucleic acids	
		○ DNA	Melphalan
		○ RNA	Mitoxantrone
		2. Enzymes	
		○ reversible effect	Edrophonium
		○ irreversible effect	Malathion
		3. Receptors	
		○ reversible effect	Prazosin
		○ irreversible effect	Phenoxybenzamine
		4. Ion channels/transporters	Calcium channel blockers; digoxin and Na^+-K^+-ATPase

Table 1 *The EIDOS mechanistic description of adverse drug effects and reactions—cont'd*

Feature		Varieties	Examples
		5. Other proteins ○ immunological proteins ○ tissue proteins	 Penicilloyl residue hapten N-acetyl-p-benzoquinone-imine (paracetamol [acetaminophen])
	(b) extracellular	1. Water 2. Hydrogen ions (pH) 3. Other ions	Dextrose 5% Sodium bicarbonate Sodium ticarcillin
	(c) physical or physicochemical	1. Direct tissue damage 2. 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)	The adverse effect (see Table 2)	–
S.	Sequela	The adverse reaction (use the Dose, Time, Susceptibility [DoTS] descriptive system)	–

Table 2 *Examples of physiological and pathological changes in adverse drug effects (some categories can be broken down further)*

Type of change	Examples
1. *Physiological changes*	
(a) Increased actions	Hypertension (monoamine oxidase inhibitors); clotting (tranexamic acid)
(b) Decreased actions	Bradycardia (beta-adrenoceptor antagonists); QT interval prolongation (antiarrhythmic drugs)
2. *Cellular adaptations*	
(a) Atrophy	Lipoatrophy (subcutaneous insulin); glucocorticosteroid-induced myopathy
(b) Hypertrophy	Gynecomastia (spironolactone)
(c) Hyperplasia	Pulmonary fibrosis (busulfan); retroperitoneal fibrosis (methysergide)
(d) Metaplasia	Lacrimal canalicular squamous metaplasia (fluorouracil)
(e) Neoplasia	
○ benign	Hepatoma (anabolic steroids)
○ malignant	
▪ hormonal	Vaginal adenocarcinoma (diethylstilbestrol)
▪ genotoxic	Transitional cell carcinoma of bladder (cyclophosphamide)
▪ immune suppression	Lymphoproliferative tumors (ciclosporin)
3. Altered cell function	IgE-mediated mast cell degranulation (class I immunological reactions)
4. Cell damage	
(a) Acute reversible damage	
○ chemical damage	Periodontitis (local application of methylenedioxymetamfetamine [MDMA, 'ecstasy'])
○ immunological reactions	Class III immunological reactions

Continued

Table 2 *Examples of physiological and pathological changes in adverse drug effects (some categories can be broken down further)—cont'd*

Type of change	Examples
(b) Irreversible injury	
○ cell lysis	Class II immunological reactions
○ necrosis	Class IV immunological reactions; hepatotoxicity (paracetamol, after apoptosis)
○ apoptosis	Liver damage (troglitazone)
5. Intracellular accumulations	
(a) Calcification	Milk-alkali syndrome
(b) Drug deposition	Crystal-storing histiocytosis (clofazimine) Skin pigmentation (amiodarone)

2. DOTS

In the DoTS system (SEDA-28, xxvii-xxxiii; 1,2) adverse drug reactions are described according to the **Dose** at which they usually occur, the **Time-course** over which they occur, and the **Susceptibility factors** that make them more likely, as follows:

- **Relation to dose**
  - Toxic reactions (reactions that occur at supratherapeutic doses)
  - Collateral reactions (reactions that occur at standard therapeutic doses)
  - Hypersusceptibility reactions (reactions that occur at subtherapeutic doses in susceptible individuals)
- **Time course**
  - Time-independent reactions (reactions that occur at any time during a course of therapy)
  - Time-dependent reactions
    - Immediate or rapid reactions (reactions that occur only when drug administration is too rapid)
    - First-dose reactions (reactions that occur after the first dose of a course of treatment and not necessarily thereafter)
    - Early tolerant and early persistent reactions (reactions that occur early in treatment then either abate with continuing treatment, owing to tolerance, or persist)
    - Intermediate reactions (reactions that occur after some delay but with less risk during longer term therapy, owing to the "healthy survivor" effect)
    - Late reactions (reactions the risk of which increases with continued or repeated exposure)
    - Withdrawal reactions (reactions that occur when, after prolonged treatment, a drug is withdrawn or its effective dose is reduced)
    - Delayed reactions (reactions that occur at some time after exposure, even if the drug is withdrawn before the reaction appears)
- **Susceptibility factors**
  - Genetic
  - Age
  - Sex
  - Physiological variation (e.g. weight, pregnancy)
  - Exogenous factors (for example the effects of other drugs, devices, surgical procedures, food, smoking)
  - Diseases

The following reactions are described in figures in SEDA-34 and SEDA-35 using the EIDOS and DoTS systems. These descriptions supersede those in previous volumes.

The following reactions have also been described in previous editions of SEDA using the DoTS system:

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Definitive (between-the-eyes) adverse drug reactions

About 30% of the papers covered in the SEDA series are classified by our authors as anecdotal (reference numbers marked with the A tag). Although anecdotes have been regarded as being of little evidential value, and rank low in evidence hierarchies, in some cases they provide striking evidence of adverse drug reactions. For example, so-called designated medical events [1], when they occur, are so often caused by drugs that a drug-event association is highly likely to be real, indeed is almost pathognomonic. Such events include Stevens–Johnson syndrome, anaphylaxis, aplastic anemia, and the form of polymorphous ventricular tachycardia known as "torsade de pointes".

An even more convincing category of anecdotal evidence consists of a small number of reports that are definitive on the basis of one or at most a few reports (so-called "between-the-eyes" reactions) [2,3]. There are four categories of such reactions, described at the foot of Table 3, which gives examples.

Table 3 *Examples of definitive anecdotal adverse drug reactions*

Event	Examples	Confirmatory tests/characteristics
1a. Extracellular deposition of drug or metabolite		
Baroliths	Barium [4]	X-ray, visual inspection; chemical analysis
Bezoars and gastrointestinal obstruction	Colestyramine [5], sucralfate, modified-release formulations, guar gum, ion exchange resins [6–8]; magnesium salts [9]; nifedipine [10,11]; psyllium [12]	Visual inspection; chemical analysis
Biliary lithiasis or pseudolithiasis	Atazanavir [13]; ceftriaxone [14]; sulindac [15,16]	Infrared spectroscopy
Nephrolithiasis, urinary crystals or debris	Aciclovir, amoxicillin, atazanavir [17], ciprofloxacin, ephedrine/guaifenesin, floctafenine [18], indinavir [19], magnesium trisilicate, methotrexate, primidone, sulfasalazine [20], sulfonamides, triamterene [21,22]; ceftriaxone [23,24]; felbamate [25]; ketamine [26]; Djenkol beans [27]	Microscopy, infrared spectroscopy, x-ray diffraction, mass spectroscopy
Respiratory damage	Minocycline [28]	Bronchial aspiration
1b. Intracellular deposition of drug or metabolite		
Calcinosis, subcutaneous	Calcium-containing heparins [29]	Histology
Conjunctival deposition	Tetracycline [30,31]	Wood's lamp

Continued

Table 3 *Examples of definitive anecdotal adverse drug reactions—cont'd*

Event	Examples	Confirmatory tests/characteristics
Corneal deposition	Fluoroquinolones [32,33]	Scanning electron microscopy, hplc, infrared spectrophotometry
	Gold [34]	Confocal microscopy
	Adrenochromes from adrenaline [35] or ibopamine [36,37]	Histology
Eyelids, deposition	Gold [38]	Histology
Gut, crystal deposition	Sodium polystyrene sulfonate [39]	Microscopy
Histiocytes, crystal deposition	Aluminium-containing vaccines [40]	Electron microprobe analysis
	Clofazimine [41]	Visual inspection, polarizing microscopy
Intraglomerular crystal deposition	Foscarnet [42]	Fourier transform infrared spectroscopy
Lipoid pneumonia	Mineral oil [43]	Gas chromatography/mass spectrometry
Lymphadenopathy	Gold [44]	Light microscopy, scanning EM
Nail deposition	Tetracycline [45]	Wood's lamp
	Clofazimine [46]	Light microscopy
Pneumonitis	Sodium polystyrene sulfonate [47–49]	
Retina, crystal deposition	Methoxyflurane [50]; canthaxanthin [51]	hplc
Skin pigmentation	Amiodarone [52]	hplc, electron microscopy, energy dispersive x-ray microanalysis
2. Specific anatomical location or pattern of injury		
Esophageal ulcers	Bisphosphonates, potassium chloride, quinidine, tetracyclines [53]	Localization to areas of esophageal lesions
Extravasation reactions	Cancer chemotherapeutic agents [54]	Anatomical contiguity to drug administration
Fulminant encephalomyelitis	Inadvertent intrathecal ionic contrast medium [55]; inadvertent intrathecal vincristine [56]	Anatomical pattern of injury
Hemangiosarcoma	Thorotrast [57]	Anatomical localization in sites of drug accumulation or persistence
Inflammatory response in a tumor	Picibanil [58]	Direct observation of application site localization
Nicolau syndrome*	Bismuth [59]; cyanocobalamin [60]; penicillins [61–64], NSAIDs [65,66]; glatiramer acetate [67,68], glucocorticoids [69]; vitamin K_1 [70,71]	
Nasopalatal damage	Topical cocaine [72]	Application site localization
Nodulosis	Apomorphine [73]	Anatomical contiguity to drug administration
Oral damage after topical application	Salicylates [74]; desloratadine [75]; ecstasy [76]; garlic [77]; metronidazole [78]	Application site localization
Small bowel obstruction	Gelatin hemostatic agent [79,80]	Application site localization

Table 3 *Examples of definitive anecdotal adverse drug reactions—cont'd*

Event	Examples	Confirmatory tests/characteristics
3. Physicochemical dysfunction or tissue damage		
Oligohidrosis	Topiramate [81] Zonisamide [82,83]	Iontophoresis Acetylcholine loading test, heat-loading test
Photosensitivity	Carbamazepine, dapsone, certain NSAIDs, triflusal [84]; fenofibrate [85]; flutamide [86]; terbinafine [87]; voriconazole [88]	Phototesting, photopatch testing
Taste disturbance	Certain NSAIDs [89]	Gustatometry, electrogustatometry
Dry mouth	Omeprazole [90]	Measurement of salivary flow
4. Infection-related		
Infection unrelated to product contamination	Bacille Calmette-Guerin [91–93]; *Escherichia coli* Nissle 1917 [94]; lactobacillus [95,96]; mumps vaccine [97]; varicella vaccine [98–100]	Polymerase chain reaction, DNA enzyme immunoassay electrophoresis, bacterial culture, strain typing, DNA fingerprinting; genomic sequencing
Infection due to product contamination	Intravenous gentamicin [101]; propofol [102]	Endotoxin assay, plasmid and restriction endonuclease analysis

*Attributable to the drug or an excipient or to the action of intramuscular injection

1. *Extracellular (1a) or intracellular (1b) tissue deposition of the drug or a metabolite* In such cases objective physicochemical testing shows that the pathological lesion is composed of the drug or a metabolite. The lesion has to be accessible for biopsy or some form of in situ examination, and the event must not have been possible in the absence of the drug.
2. *A specific anatomical location or pattern of injury* Here the location or pattern of damage is sufficiently specific to attribute the effect to the drug without the need for implicit judgment or formal investigation. The mechanism of injury can be related to either physicochemical or pharmacological properties of the drug.
3. *Physiological dysfunction or direct tissue damage that can be proved by physicochemical testing* This group includes adverse events that involve physiological dysfunction or tissue damage for which documentation by physicochemical testing is feasible.
4. *Infection as a result of administration of a potentially infective agent or because of demonstrable contamination* Adverse drug reactions related to infections can be due to contamination of the treatment or to a product that consists of live microbes. The infecting organism has to be proved to be the same as the organism contained in the product or contaminating the batch of product.

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