ADR & ADE

ADVERSE DRUG REACTION & ADVERSE DRUG EVENT

- The World Health Organization (WHO) defines an ADE as “any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment” (WHO 2005).
- The WHO defines an ADR as “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 the modification of physiologic function.” An ADR is a type of ADE whose cause can be directly attributed to a drug and its physiologic properties.

National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines ADE as :

“Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.”

ADVERSE DRUG REACTION ‖ ADVERSE DRUG EVENT ‖ ADVERSE DRUG EFFECT

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Traditionally, ADRs have been classified into two types:

I. Type A reactions

Sometimes referred to as **augmented reactions** – which are 'dose-dependent' and predictable on the basis of the pharmacology of the drug

II. Type B reactions

Bizarre reactions – which are idiosyncratic and not predictable on the basis of the pharmacology.

This is also known as the Rawlins-Thompson classification

REACTION	TYPE A 'AUGMENTED'	TYPE B 'BIZARRE'
Pharmacologically predictable	Yes	No
Dose-dependent	Yes	Not clearly
Incidence	Common	Uncommon
Detection	Early in clinical development	Post-licensing
Mortality	Low	High
Management	Reduce dose	Discontinue therapy

Type A (pharmacological; 85–90%)	side effects	
	drug interactions	
	others	
Type B (hypersensitivity)	nonspecific mechanisms	defective or absent enzymes
		cytokine dysbalance
		dysbalance of inflammatory mediators
		nonspecific mast cell degranulation
	specific immune reactions (true allergies)	type I: IgE mediated
		type II: IgG-mediated cytotoxicity
		type III: immune complex deposition
		type IV: T cell mediated: (a) monocytic inflammation (b) eosinophilic inflammation (c) cytotoxic T cells (d) neutrophilic inflammation

Hausmann, Oliver & Schnyder, Benno. (2012). Etiology and Pathogenesis of Adverse Drug Reactions. Chemical immunology and allergy. 97. 32-46. 10.1159/000335614.

Subsequently, two further types of reaction were added: reactions related to both dose and time, and delayed reactions, later labelled types C and D.

The last of these categories can be split into two: time-related reactions and withdrawal effects.

III. TYPE C

IV. TYPE D

V. TYPE E

More recently, a sixth category has been proposed: unexpected failure of therapy

VI. TYPE F

Type of reaction	Mnemonic	Features	Examples	Management
A: Dose-related	Augmented	• Common • Related to a pharmacological action of the drug • Predictable • Low mortality	• Toxic effects: Digoxin toxicity; serotonin syndrome with SSRIs • Side effects: Anticholinergic effects of tricyclic antidepressants	• Reduce dose or withhold • Consider effects of concomitant therapy
B: Non-dose-related	Bizarre	• Uncommon • Not related to a pharmacological action of the drug • Unpredictable • High mortality	• Immunological reactions: Penicillin hypersensitivity • Idiosyncratic reactions: Acute porphyria Malignant hyperthermia Pseudoallergy (eg, ampicillin rash)	• Withhold and avoid in future
C: Dose-related and time-related	Chronic	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	• Reduce dose or withhold; withdrawal may have to be prolonged
D: Time-related	Delayed	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia	• Often intractable
E: Withdrawal	End of use	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)	• Reintroduce and withdraw slowly
F: Unexpected failure of therapy	Failure	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers	• Increase dosage • Consider effects of concomitant therapy

SSRIs=serotonin-selective reuptake inhibitors.

(Source: Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000 Oct 7;356(9237):1255-9.)