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## Review Article

# Management of adverse drug reactions: A review

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### ABSTRACT

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as “a response to a medication that is noxious and unintended used in man to treat”. An adverse drug reaction (ADR) can be defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product’.

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## 1. Basics of Adverse Drug Reactions

Adverse drug reactions (ADRs) – unintended, harmful events attributed to the use of medicines. A careful medication history can assist a prescriber in understanding the patient’s previous experiences with drug treatment, particularly in identifying previous ADRs that may preclude re-exposure to the drug.<sup>1,2</sup>

### 1.1. History

Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off- label in addition to the authorised use of a medicinal product in normal doses.<sup>2</sup> Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice.<sup>3–5</sup>

Medicines that have been particularly implicated in ADR-Fatal ADRs, when they occur, are often attributable to haemorrhage, the most common suspected cause being an *antithrombotic/anticoagulant co-administered with a non-*

*steroidal anti- inflammatory drug (NSAID).*<sup>4</sup>

### 1.2. Pharmacovigilance

The term Pharmacovigilance is the science and activities related to the detection, evaluation, understanding and prevention of adverse drug reactions and other related problems.<sup>6</sup> According to WHO, Pharmacovigilance is a set of practices aiming at the identification, understanding and assessment of the risks associated with drugs.<sup>7</sup>

Pharmacovigilance has been defined by the WHO (2002) as the ‘science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug -related problems.’<sup>8</sup> Its main purpose is to reduce the risk of drug-related harm to the patient. It has an important role in the rational use of medicines, as it provides the basis for assessing safety of medicines.<sup>8</sup>

The main objective of Pharmacovigilance is to regulate and ensure the safety & efficacy after the entry of the new drug molecule into the market for the treatment of diseases of the general population with different medical conditions. Recently the concern of Pharmacovigilance has been widened to include herbals, medicines, blood products, biological products, medical devices and vaccines<sup>7</sup>

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### 1.3. Pharmacovigilance support safe and appropriate use of by

1. Promoting the detection of Previously unknown ADRs and interactions.
2. Identifying the risk factors for the development of ADRs.
3. Estimating the quantitative methods /risk analysis.<sup>9</sup>

## 2. Classification of Adverse Drug Reaction

### 2.1. Based on frequency of occurrence<sup>10,11</sup>

Based on the type of adverse drug reaction<sup>10,11</sup>

### 3. Definition related to the Adverse drug reaction:<sup>15,16</sup>

1. *Adverse drug reaction:* It is any noxious, unintended and unexpected effect of a drug that occurs at a dose used in humans for prophylaxis, diagnosis, and therapy of a disease. Requires special treatment or decreases in dose.

2. *Adverse Effect:* It is a noxious and unintended effect that may occur during the treatment With pharmaceutical product .Not requires treatment.

3. They are related to the use of drugs

4. *Drug recall:* It is a action taken by firm to remove product from market.<sup>17</sup>

5. *WHO drug dictionary:* It is a International classification of drug providing name of medicinal Product, use in different countries with all active ingredients.<sup>18</sup>

## 4. Categories of Adverse Drug Reaction

### 4.1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. Generally, they are not serious, can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients. Reduction in dose, usually ameliorates the symptoms. A side effect may be based on the same action as the therapeutic effect.

*Example:* Atropine is used in preanaesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect.<sup>8</sup>

### 4.2. Secondary effect

These are indirect consequences of a primary action of the drug.

*EX:* Suppression of bacterial flora by tetracyclines paves the way for superinfections .

### 4.3. Toxic effects

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use. The manifestations are predictable and dose related.

*EX:* drug induced tissue damage (hepatic necrosis from paracetamol overdosage).<sup>8,19</sup>

Another action of the drug can also be responsible for toxicity

### 4.4. Examples are

1. Morphine (analgesic) causes respiratory failure in overdosage.
2. Imipramine (antidepressant) overdose causes cardiac arrhythmia.
3. Streptomycin (antitubercular) causes vestibular damage on prolonged use.

### 4.5. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug.

### 4.6. Examples

1. A single dose of triflupromazine induces muscular dystonia in individuals, specially children.
2. Only few doses of carbamazepine may cause ataxia in some people.
3. One tablet of chloroquine may cause vomiting and abdominal pain in an occasional patient.

### 4.7. Idiosyncrasy

It is genetically determined abnormal reactivity to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction.

### 4.8. Examples are

1. Barbiturates cause excitement and mental confusion in some individuals.
2. Quinine/quinidine cause cramps, diarrhoea, purpura, asthma and vascular collapse in some patients.
3. Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

### 4.9. Drug allergy

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug, generally occur even with much smaller doses and have a different time course of onset and duration. This is also called drug hypersensitivity.

### 4.10. Drugs frequently causing allergic reactions

1. Penicillins

**Table 1:** Frequency of occurrence

Sr. no.	Category	Frequency	Example
1	Very common	>10%	Dizziness, fatigue, tiredness.
2	Common (frequent)	>1% and <10%	Sedation, memory problems, Depression.
3	Uncommon (infrequent)	>0.1% and <1%	Skin rash
4	Rare	>0.01% and <0.1%	Stevens Johnson syndrome (Sulphonamide).
5	Very rare	<0.01%	Aplastic anemia (phenytoin).

**Table 2:** Types of adverse drug reaction

Sr. no.	Type	Description	Examples
1	TypeA (Augmented)	Predicted, Dose dependent, severity increases with increase in dose. <sup>12</sup>	Hypotension by beta-blockers & hypoglycaemia caused by insulin .
2	TypeB (Bizarre)	Unpredictable, rare, idiosyncratic, mechanisms are unknown, unrelated to the dose. <sup>13</sup>	Hepatitis caused by halothane & aplastic anaemia caused by chloramphenicol .
3	TypeC (Continuous drug use)	Irreversible, unexpected, unpredictable. <sup>14</sup>	Dementia by anticholinergic medications .
4	TypeD (Delayed)	Delayed occurrence of ADRs.	Ophthalmopathy after chloroquine.
5	TypeE (End of Dose)	Withdrawal reactions.	Seizures on alcohol or benzodiazepines withdrawal.
6	TypeF (Failure of therapy)	Therapeutic failure of drug.	Accelerated hypertension because of improper therapy .

2. Salicylates
3. Cephalosporins
4. Carbamazepine
5. Sulfonamides
6. Allopurinol
7. Tetracyclines
8. ACE inhibitors
9. Quinolones
10. Methyldopa
11. Antitubercular drugs
12. Hydralazine
13. Phenothiazines
14. Local anaesthetics

#### 4.11. Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation.

#### 4.12. The reactions are of two types

(a) *Phototoxic* Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn-like), i.e. erythema, edema, blistering which have fast onset and shorter duration after exposure ends. This is followed by hyperpigmentation and desquamation.

The lesions may be more severe with larger doses of the drug.

The shorter wave lengths (290–320 nm, UV-B) are responsible for the phototoxic reactions.

#### 4.13. Example

Drugs involved in acute phototoxic reactions are tetracyclines (especially demeclocycline) and tar products.

#### 4.14. Photoallergic

Drug or its metabolite induces a cell mediated immune response which on exposure to light of longer wave lengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture that may persist long after exposure. Rarely antibodies mediate photoallergy and the reaction takes the form of immediate flare, itching and wheal on exposure to sun.

#### 4.15. Example

Drugs involved are sulfonamides, sulfonyleureas, griseofulvin, chlorpromazine, carbamazepine.

#### 4.16. Drug dependence

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, recreation, withdrawal from reality, social adjustment, etc. Drug dependence is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs, often in the face of known risks to health.

#### 4.17. Psychological dependence

It is said to have developed when the individual believes that optimal state of wellbeing is achieved only through the

actions of the drug. The subject feels emotionally distressed if the drug is not taken.

#### 4.18. Physical dependence

It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic withdrawal (abstinence) syndrome.

#### 4.19. Drug abuse

Refers to use of a drug by self-medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time.

#### 4.20. Drug addiction

It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities. Even after withdrawal most addicts tend to relapse.

#### 4.21. Drug habituation

It denotes less intensive involvement with the drug, so that its withdrawal produces only mild discomfort. Consumption of tea, coffee, tobacco, social drinking are regarded Habituation.

#### 4.22. Drug withdrawal reactions

Apart from drugs that are usually recognised as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse effects

#### 4.23. Example

1. Severe hypertension, restlessness and sympathetic overactivity may occur shortly after discontinuing clonidine.
2. Worsening of angina pectoris, precipitation of myocardial infarction may result from stoppage of  $\beta$  blockers.

### 5. Frequency of Seizures May Increase on Sudden Withdrawal of An Antiepileptic

#### 5.1. Teratogenicity

It refers to the capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. The placenta does not constitute a strict barrier, and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems and in contrast to adults, drug effects are often irreversible.

#### 5.2. Example

Thalidomide disaster cause phocomelia to babies born (Sea like limbs).<sup>20</sup>

### 6. Mutagenicity and Carcinogenicity

It refers to capacity of a drug to cause genetic defects and cancer respectively. Usually oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Covalent interaction with DNA can modify it to induce mutations. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens.

#### 6.1. Drug induced diseases

These are also called iatrogenic (physician induced) diseases, and are functional disturbances (disease) caused by drugs.

#### 6.2. Example

1. Peptic ulcer by salicylates and corticosteroids.
2. Parkinsonism by phenothiazines and other antipsychotics.
3. Hepatitis by isoniazid.

### 7. Adverse Drug Reaction Management

1. Recognition/Identification Of Adverse Drug Reaction
2. Reporting
3. Prevention of Adverse Drug Reaction
4. Management of Adverse Drug Reaction

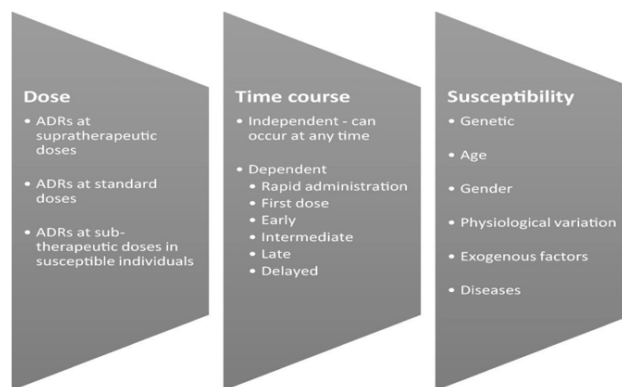


Figure 1: ADR management

### 8. Recognition/Identification Of Adverse Drug Reaction

1. Ensure, medicine received & actually taken by the patient at the dose advised.

2. Verify the onset of suspected ADR is after taking the drug.
3. Determine the time interval between drug taken – onset of event.
4. Evaluate the suspected ADR after discontinuing the drug / reduced dose, monitor status.
5. Analyse the alternate cause (other than the drug).
6. Use experienced physician opinion & information PV center.
7. Report the ADR.

6. ADRs occurring from overdose or medication error.

### 8.3. Information required for ADR case reporting

#### 8.3.1. Patient information

1. Patient identifier
2. Age at time of event or date of birth
3. Gender
4. Weight

#### 8.3.2. Product problems/Adverse effect

1. Description of event or problem
2. Date of event
3. Date of this report
4. Relevant tests/laboratory data (if available)
5. Other relevant patient information/history.<sup>22</sup>

#### 8.3.3. Suspected medication (s)

1. Name ( brand name)
2. Dose, frequency
3. Route used
4. Therapy date
5. Diagnosis for use
6. Event abated after use stopped or dose reduced
7. Batch number
8. Expiration date
9. Event reappeared after reintroduction of the treatment.<sup>23</sup>

#### 8.3.4. Reporter

1. Name
2. Address and telephone number
3. Speciality and occupation

## 9. WHO Should Report

1. Doctors
2. Pharmacists
3. Assistant medical officers
4. Clinical officers
5. Pharmaceutical assistants
6. Traditional medicine practitioners
7. Others health care providers

### 9.1. When to report

1. Any suspected ADR should be reported as soon as possible.
2. Delay in reporting will make reporting inaccurate and unreliable.
3. If possible, report while the patient is still in the health facility this gives a chance to reporter to clear any ambiguity by re-questioning or examining the patient.

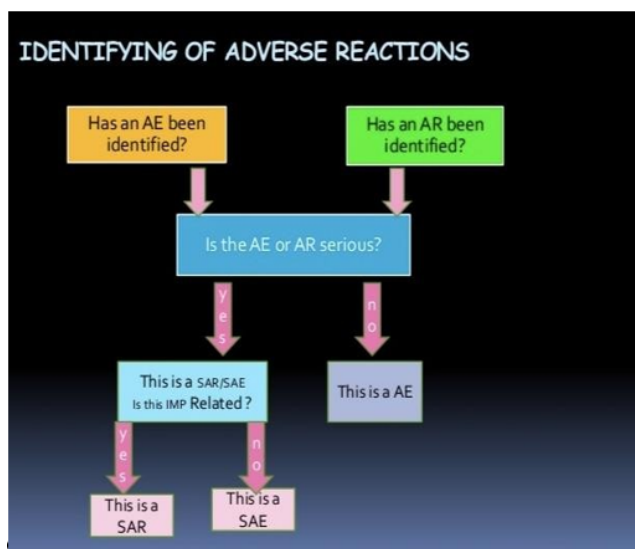


Figure 2: Identifying AD

### 8.1. Reporting

Adverse drug reaction reporting helps the drug monitoring system to detect the unwanted effects of those drugs which are already in the market.

ADR Reporting is a process of continuously monitoring of undesirable effect suspected to be associated with use of medical products. ADR reporting covers all pharmaceutical products, biological, herbal drugs, cosmetics and medical devices.<sup>21</sup>

### 8.2. What to report

1. Any undesirable adverse event suspected to be associated with use of drug.
2. Include - All ADRs as a result of prescription and non-prescription.
3. All ADRs – irrespective of the used (acc with PI provided by company).
4. Unexpected reactions - regardless of their nature or severity.
5. ADRs-in special field – drug abuse, drug use – pregnancy / lactation.

## 9.2. How to report

CDSCO suspected ADR Reporting Form.<sup>24,25</sup>

DEPARTMENT OF CLINICAL PHARMACY, JSS HOSPITAL, RAMANUJA ROAD, MYSORE-04	
NOTIFICATION OF A SUSPECTED ADVERSE DRUG REACTION	
Patient's Name : .....	Age : ..... Sex : .....
Address & Contact Number : .....	
Prescriber : .....	
Suspected drug(s) : .....	
Date of drug started : .....	
Date of adverse reaction started : .....	
Brief description of the reaction : .....	
Name of the reporting Community Pharmacist : .....	
Address & Contact No. : .....	
Signature : .....	Date : .....
Please return this to the Department of Clinical Pharmacy or call (2421218) so that a clinical pharmacist can investigate and document the suspected adverse drug reaction (ADR) as soon as possible.	

## 10. Where to Report

1. Please return the completed form to the nearest Adverse drug reaction Monitoring Centre (AMC) or to National Coordinating Centre.
2. The Uppsala Monitoring Centre (Sweden) is the international collaborating centre. In India, the Central Drugs Standard Control Organization (CDSCO) is coordinating the pharmacovigilance programme, under which peripheral, regional and zonal monitoring centres have been set up along with a National Pharmacovigilance advisory committee.
3. The pharmacovigilance centres collect, communicate and disseminate ADR data by linking with hospitals as well as practitioners and are also expected to provide expertise for assessing causality and severity of ADRs.
4. The information is submitted to the Steering Committee of PvPI constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.<sup>21,26</sup>

## 11. Prevention of Adverse Drug Reaction

1. (a) Anticipation by patient monitoring Ex- anemia- due to deficiency of G6PD, check the condition.
- (b) Anticipation of dosage reeducation Ex- impaired renal / liver function – dosage should reduce.
- (c) Monitoring the serum levels(drug) Ex- theophylline, aminoglycosides.

- (d) Monitoring of pharmacological activity (extensive of Pharmacology activity) Ex- diuretics- to promote salt & water loss, but causes electrolyte depletion & dehydration.<sup>27</sup>
- (e) Minimizing of non-preventable- Idiosyncratic / hypersensitivity not preventable.
- (f) Can be done by careful observation / monitoring of patient Ex- patient with meningitis

- Should be with penicillin. Chemotherapy – nausea<sup>28</sup>

## 12. Management of Adverse Drug Reaction

Confirmation of the ADRs: indicate what assisted in confirming the suspected adverse reactions.

### 12.1. For example

1. Drug reactions confirmed by disappearance of the reaction after stopping administration of the drug or reducing the doses.
2. Recovery on withdrawal of suspected drug(s) if no other drug is withdrawn and no therapy given.
3. Recovery follows treatment of the reaction in addition to withdrawal of drug.

Mention the criteria for regarding the reaction as serious

Mention any treatment given to the patient after experiencing the ADRs.

Outcome: indicate the outcome of the adverse reaction by marking X in the appropriate box with dates.<sup>29</sup>

## 13. Aim and Objectives

1. To disclose the quality and frequency of ADRs and to identify the risk factors that can cause the adverse reactions.
2. To improve patient care and safety in relation to the use of medicines.
3. To improve public health and safety in relation to the use of medicines.
4. To identify new reactions, record the frequency with which they are reorted.
5. To evaluate factors that may increase risk of ADR.
6. To provide information to prescribers with a view to preventing future ADRs.
7. To prevent predictable adverse effects and helps in measuring ADR incidence.
8. To get information about quality and safety of Pharmaceutical products.
9. To detect, collect, assess, and monitor the adverse effect.

## 14. Conclusion

1. Herein we have discussed the identification, management and reporting of ADRs.

2. We have described how modern technology is changing the way that ADRs are predicted, prevented, detected and managed, and how we continue to try to improve these processes with technological advances.

## 15. Source of Funding

None.

## 16. Conflict of Interest

None.

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