The occurrence and importance of adverse effects of medicines is underestimated and underreported

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Introduction

- The risk of adverse medicine effects is necessarily an inherent risk for all drug therapy
- It is modulated by several factors:
- -the dose and frequency of administration
- -genotype
- - pharmacokinetic characteristics of special populations, such as paediatric and geriatric patients and those with hepatic or renal impairment

Introduction

Key definitions

- **Adverse effect** – is an undesirable and un-intended effect of a drug, including lack of efficacy
- Occurs at any dose and can also result from overdose, misuse or abuse of medicine.
- Adverse effects are then, always harmful consequences from the use of medicinal products.
- The word “effect” is used interchangeably with “reaction”.
- .

Introduction

Side effects- are predictable effects from the use of a medicinal product.

- Unintended effect of a pharmaceutical product occurring at therapeutic doses and is related to its pharmacological properties.
- May be well known and even expected and require little or no change in patient management

Serious adverse effect

- Any untoward medical occurrence at any dose and results in death, requires hospital admission or prolonged hospital stay
- Results in persistent or significant disability, or is life threatening

Two common types of ADRs

- **Type A** reactions are expected amplification of a drug's known pharmacologic effects. They are usually dose-dependent, predictable and in most cases preventable. e.g Hypotension due to antihypertensive medicines and ototoxicity due to aminoglycosides
- **Type B** reactions are idiosyncratic and tend to be unrelated to the known pharmacologic action of the medicine. They are not dose related, unpredictable, uncommon. e.g anaphylaxis reaction to the administration of penicillin.

The impact of ADRs

- Studies conducted in developed countries have shown that adverse effects from medicines are a significant cause of hospital admissions, prolong hospital stay and consequently increase the cost of disease management in patients
- ADRs may also trigger prescription cascades , which can contribute to the increase in costs
- Main direct costs of ADRs are: wages, disposable goods and medicines
- Indirect costs: costs incurred by patients and their caregivers, such as missed days from work and /or morbidity such as anxiety due to the ADR episode

Identifying ADRs

- **Premarketing clinical trials**
  - Animal studies, human studies—Phases I, II, III
  - Randomised clinical trials

- **Post-marketing surveillance**
  - Spontaneous reporting
  - Post-marketing clinical trials—Phase IV
  - Other methods—observational studies, meta-analysis, case reports

Spontaneous Reports

- Best method for detecting new ADRs
- Necessary because many ADRs are not detected in pre- or post-marketing studies
- Initiated by medical practitioners, pharmacists, nurses, patients
- Problems include underreporting,
  - inaccurate reporting that may not show causality

Actions for Newly Discovered ADRs

- "Dear Doctor" letters—describe a new safety concern about a particular medicine
- Package insert revisions
  - For *significant* safety concerns
  - Manufacturers must change the official labeling and the package insert to reflect the new safety concern
  - Typically approved by the regulatory authority
- Medicine recalls (voluntary and compulsory)
  - For *serious* safety concerns
  - May be voluntary or imposed by the regulatory authority

Table 1 List of drugs withdrawn for safety reasons in all EU member states between 2002 and 2011 grouped by adverse drug reaction or safety concern

Drug name	Drug class or use	Year first marketed	Year of withdrawal	Length of time on market (years)	Adverse reaction or safety concern
Rofecoxib	NSAID (COX-2 inhibitor)	1999	2004	5	Thrombotic events
Thioridazine	Neuroleptic (α-adrenergic and dopaminergic receptor antagonist)	1958	2005	47	Cardiac disorders
Valdecoxib	NSAID (COX-2 inhibitor)	2003	2005	2	Cardiovascular and cutaneous disorders
Rosiglitazone	Antidiabetic treatment (PPAR agonist)	2000	2010	10	Cardiovascular disorders
Sibutramine	Treatment of obesity (serotonin-noradrenaline reuptake inhibitor)	1999	2010	11	Cardiovascular disorders
Orciprenaline	Sympathomimetic (non-specific β-agonist)	1961	2010	49	Cardiac disorders
Benfluorex	Anorectic and hypolipidaemic	1974	2009	35	Heart valve disease—Pulmonary hypertension
Clobutinol	Cough suppressant (centrally acting)	1961	2007	46	QT prolongation
Buflomedil	Vasodilator (α1 and α2 receptor antagonist)	1974	2011	37	Neurological and cardiac disorders (sometimes fatal)
Veralipride	Neuroleptic (and dopaminergic receptor antagonist)	1979	2007	28	Neurological and psychiatric disorders
Rimonabant	Treatment of obesity (cannabinoid receptor antagonist)	2006	2008	2	Psychiatric disorders
Carisoprodol	Muscle relaxant	1959	2007	48	Intoxication—Psychomotor impairment—Addiction—misuse
Acepromethazine + Acepromazine + Clorazepate	Hypnotic	1988	2011	23	Cumulative adverse effects—misuse—fatal side effect
Dextropropoxyphene	Opioid painkiller	~1960	2009	49	Fatal overdose
Nefazodone	Antidepressant	1994	2003	9	Hepatotoxicity
Ximelagatran/melagatran	Anticoagulant (thrombin inhibitor)	2003	2006	3	Hepatotoxicity
Lumiracoxib	NSAID (COX-2 inhibitor)	2003	2007	4	Hepatotoxicity
Sitaxentan	Antihypertensive (endothelin receptor antagonist)	2006	2010	4	Hepatotoxicity
Bufexamac	NSAID	~1970	2010	40	Contact allergic reactions

EU, European Union; NSAID, non-steroidal anti-inflammatory drug.

Incidence

- According to the Global Burden of Disease, adverse effects from medical treatment resulted in over 140,000 deaths in 2013, up from 94,000 in 1990.
- One fifth of patients readmitted to hospital within one year of discharge from their index admission were re-admitted due to an ADR in the UK
- ADRs resulted in approximately 250,000 admissions a year in the United Kingdom

Incidence

- A meta-analysis of 69 prospective and retrospective studies conducted in various regions of the world involving 419, 000 patients found that approximately 6.7% of all hospitalisations were as a result of ADRs
- The proportion of patients admitted with ADRs ranges from 2% to 21.4%, where as between 1.7% and 25.1% of hospital inpatients are reported to have developed an ADR while in hospital (Mehta et al, 2007)
- An observational study carried out in the Western Cape, estimated that 6.3% of hospitalised patients were admitted as a direct result of an ADR

Risk of adverse effects of medicines

- According to Davies et al, (2010) in the UK-admission to the medical ward, elderly age and prescription of anti-platelet agents or diuretics were risks factors for re-admission due to ADRs.
- In South Africa cardiovascular medicines and antiretroviral therapy contributed the most to community acquired ADRs at the time of hospital admission while medicines used for opportunistic infections such as antifungals, antibiotics and anti-tuberculosis medicine were mostly implicated in hospital acquired ADRs (Mehta et al,2007).

A cross-sectional survey at 4 hospitals in South Africa (Moutan et al, 2016)

- 8.4%(164 of 1904) of admissions were ADR related. ADR related admission was independently associated (P<0.02) with female sex, increasing drug count, increasing comorbidity score and use of antiretroviral therapy (ART) if HIV infected.
- The most common ADRs were: renal impairment, hypoglycaemia, liver injury, and haemorrhage.
- Tenofovir, insulin, rifampicin and warfarin were most commonly implicated medicines in the four ADRs
- ARTs, ATT and/ or cotrimoxazole were implicated in 34% of the ADR related admissions

Reasons for under-reporting (medical practitioners)

- Medical specialty the professional characteristics associated with underreporting in 76% of studies involving physicians
- 95 % -Ignorance (only severe ADRs need to be reported)
- 72 % -diffidence (fear of appearing ridiculous for reporting merely suspected ADR)
- 77 % - lethargy- (lack of interest or time to find a report card and other excuses)
- 67%- indifference and insecurity (it is nearly impossible to determine whether or not a drug is responsible for a particular ADR) causality

Reasons for under-reporting by Medical practitioners

- 47 % - Complacency (only safe medicines are allowed on the market) Lopez-Gonzaele E, Herdeiro MT and Figueiras A. 2009. Determinants of under-reporting of adverse drug reactions: a systemic review. Drug Saf; 32(1):19-31
- Forgetting to report
- The ADR is already Known

The knowledge and attitudes of health professional are strongly related with reporting in many studies.

Reasons for under-reporting by pharmacists

- Reporting probability proved higher among hospital versus community pharmacists
- Attitudes to ADRs were strongly associated with reporting probability
- A decrease in the following attitudes increased the probability of reporting
- “Really serious ADRs are well documented by the time a drug is marketed”
- “I would report an ADR if I were sure that it was related to the use of a particular drug”

Reasons for under-reporting by pharmacists

- “it is only necessary to report serious or unexpected ADRs”
- “I do not have time to think about the involvement of the drug or other causes in ADRs”
- ADR under-reporting is strongly associated with certain attitudes, which could be minimised through educational interventions targeted at changing them.

Conclusion

- Many adverse drug events are preventable. Patients and caregivers can help reduce the risk of harm from medicines by learning about medication safety
- Identification and management of ADRs should be considered in patient management programmes and should be emphasized in healthcare worker training programmes.
- Healthcare professional's Knowledge, beliefs, behaviour and motivation play an important role in ADR reporting

Conclusion

- Detection of ADRs in hospitals provides an important measure of the burden of drug related morbidity on the health care system.

References

- Mehta et al. 2007. adverse drug reactions in adult medical inpatients in a South African hospital serving a community with high HIV prevalence: Prospective Cohort study. BJCP
- Chan et al. 2008. Cost of evaluation of Adverse drug reactions in Hospitalised patients in Taiwan: A Prospective, Descriptive , Observational study
- Moutan et al. 2016. Adverse drug reactions causing admissions to medical wards: A cross-sectional Survey at 4 Hospitals in South Africa. Medicine;95 (19) e 3437
- Blockman M. 2015.adverse Drug events Why Care. Allergy & Clinical Immunology; 28 (4)
- Davies et al. 2010. emergency readmissions to hospital due to adverse drug reactions within I year of the index admission. BJCP
- Lopez-Gonzaele E, Herdeiro MT and Figueiras A. 2009. Determinants of under-reporting of adverse drug reactions: a systemic review. Drug Saf; 32(1):19-31

- McNaughton R, Huet G, and Shakir S. 2014. An investigation into drug products withdrawn from the EU market between 2002 and 2011 for saftey reasons and the evidence used to support the decision making. BMJ. e004221