Clinical Analysis of Adverse Drug Reactions

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Objectives

- **Define adverse drug reactions**
- **Discuss epidemiology and classification of ADRs**
- **Describe basic methods to detect, evaluate, and document ADRs**
- **FDA adverse drug reaction initiatives**

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Definition - WHO

– **WHO**
  - **response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function**

  - **Purposely excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors**

Definition – FDA

- **Adverse drug reaction according to the U.S. Food and Drug Administration (FDA)**
  - **Any undesirable experience associated with the use of a medical product in a patient.**

Adverse Drug Events

Adapted from Bates et al.

Graphic illustration showing a large circle entitled “Medication Errors (preventable)” with a smaller half-overlapping circle entitled “Adverse Drug Events (ME & ADR)”.

Adverse Drug Event: preventable or unpredicted medication event---with harm to patient

Pharmacovigilance

- **The science of adverse drug reactions**
- **detection, assessment, understanding and prevention of adverse effects**
- **Regulatory agencies, pharmaceutical companies and individual healthcare providers enact a system**

Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients*
- 6.7% incidence of serious ADRs*
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions
- 30% to 60% are preventable

*JAMA. 1998;279:1200-1205.

Epidemiology

- **82% of American adults take at least one medication and 29% take five or more**
- **700,000 emergency department visits and 120,000 hospitalizations are due to ADEs annually**
- **$3.5 billion is spent on extra medical costs of ADEs annually**
- **At least 40% of costs of ambulatory (non-hospital settings) ADEs are estimated to be *preventable***

Increase in Adverse Drug Events

- **Development of new medications**
- **Discovery of new uses for older medications**
- **Aging American population**
- **Increase in the use of medications for disease prevention**
- **Increased coverage for prescription medications**

Classification

- **Onset**
- **Severity**
- **Type**

Classification

- **Onset of event:**
  - **Acute**
    within 60 minutes
    Anaphylactic shock, bronchoconstriction
  - **Sub-acute**
    1 to 24 hours
    Rash, serum sickness, abx associated colitis
  - **Latent**
    > 2 days
    Eczematous eruptions, tardive dyskinesia

Classification – Severity

Severity of reaction:

- **Mild**
  - **bothersome but requires no change in therapy**
  - **Metallic taste with metronidazole**
- **Moderate**
  - **requires change in therapy, additional treatment, hospitalization**
  - **Amphotericin induced hypokalemia**
- **Severe**
  - **disabling or life-threatening**
  - **QT interval prolongation, kidney failure**

Classification - Severity

- **FDA Defines Serious ADR**
  - **Result in death**
  - **Life-threatening**
  - **Require hospitalization**
  - **Prolong hospitalization**
  - **Cause disability**
  - **Cause congenital anomalies**
  - **Require intervention to prevent permanent injury**

Classification

- **Type A**
  - **extension of pharmacologic effect**
  - **often predictable and dose dependent**
  - **responsible for at least two-thirds of ADRs**
  - **e.g., propranolol and heart block, anticholinergics and dry mouth**

- **Type B**
  - **idiosyncratic or immunologic reactions**
  - **rare and unpredictable**
  - **e.g., chloramphenicol and aplastic anemia**
  - **Rash caused by beta lactam antibiotics**

Classification

- **Types of allergic reactions**
- **Type I - immediate, anaphylactic (IgE)**
- **e.g., anaphylaxis with penicillins**
- **Type II - cytotoxic antibody (IgG, IgM)**
- **e.g., methyldopa and hemolytic anemia**
- **Type III - serum sickness (IgG, IgM)**
- **antigen-antibody complex**
- **e.g., procainamide-induced lupus**
- **Type IV - delayed hypersensitivity (T cell)**
- **e.g., contact dermatitis**

Common Causes of ADRs

- **Antibiotics**
- **Antineoplastics***
- **Anticoagulants**
- **Cardiovascular drugs***
- **Hypoglycemics**
- **Antihypertensives**
- **NSAID/Analgesics**
- **Diagnostic agents**
- **CNS drugs***

***account for 69% of fatal ADRs**

Body Systems Commonly Involved

- **Hematologic**
- **CNS**
- **Dermatologic/Allergic**
- **Metabolic**
- **Cardiovascular**
- **Gastrointestinal**
- **Renal/Genitourinary**
- **Respiratory**
- **Sensory**

ADR Risk Factors

- **Age (children and elderly)**
- **Multiple medications**
- **Multiple co-morbid conditions**
- **Inappropriate medication prescribing, use, or monitoring**
- **End-organ dysfunction**
- **Altered physiology**
- **Prior history of ADRs**
- **Extent (dose) and duration of exposure**
- **Genetic predisposition**

ADR Detection

- **Subjective report**
  - **patient complaint**
- **Objective report:**
  - **direct observation of event**
  - **abnormal findings**
    - » **physical exam**
    - » **laboratory test**
    - » **diagnostic procedure**

ADR Detection

- **Medication order screening**
  - **abrupt medication discontinuation**
  - **abrupt dosage reduction**
  - **orders for “tracer” or “trigger” substances**
  - **orders for special tests or serum drug concentrations**
- **Spontaneous reporting**
- **Medication utilization review**
  - **Computerized screening**
  - **Chart review and concurrent audits**

ADR Detection in Clinical Trials

- **Methods**
  - **Standard laboratory tests**
  - **Diagnostic tests**
  - **Complete history and physical**
  - **Adverse drug event questionnaire**
    Extensive checklist of symptoms categorized by body system
    Review-of-systems approach
    Qualitative and quantitative

ADR Detection in Clinical Trials

Limitations

- **exposure limited to few individuals**
  rare and unusual ADRs not detected
  3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty
- **exposure is often short-term**
  latent ADRs missed
- **external validity**
  may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

Preliminary Assessment

- **Preliminary description of event:**
  - **Who, what, when, where, how?**
  - ***Who* is involved?**
  - ***What* is the most likely causative agent?**
    - **Is this an exacerbation of a pre-existing condition?**
    - **Alternative explanations / differential diagnosis**
  - ***When* did the event take place?**
  - ***Where* did the event occur?**
  - ***How* has the event been managed thus far?**

Preliminary Assessment

- **Determination of urgency:**
  - **What is the patient's current clinical status?**
  - **How severe is the reaction?**

- **Appropriate triage:**
  - **Acute (ER, ICU, Poison Control)**

Detailed Description of Event

- **History of present illness**
- **Signs / Symptoms:**
  - P**rovoking or palliative factors**
  - **Quality (character or intensity)**
  - **Response to treatment,**
  - **Severity / extent, Site (location)**
  - **Temporal relationship (onset, duration, frequency)**
  - **Other associated signs and symptoms**

Pertinent Patient/Disease Factors

- **Demographics**
  - **age, race, ethnicity, gender, height, weight**
- **Medical history and physical exam**
  - **Concurrent conditions or special circumstances**
    e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - **Recent procedures or surgeries and any resultant complications**
    e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

- **End-organ function**
- **Review of systems**
- **Laboratory tests and diagnostics**
- **Social history**
  tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
- **Pertinent family history**
- **Nutritional status**
  special diets, malnutrition, weight loss

Pertinent Medication Factors

- **Medication history**
  - **Prescription medications**
  - **Non-prescription medications**
  - **Alternative and investigational therapies**
  - **Medication use within previous 6 months**
  - **Allergies or intolerances**
  - **History of medication reactions**
  - **Adherence to prescribed regimens**
  - **Cumulative mediation dosages**

Pertinent Medication Factors

- **Medication**
  - **Indication, dose, diluent, volume**
- **Administration**
  - **Route, method, site, schedule, rate, duration**
- **Formulation**
  - **Pharmaceutical excipients**
    e.g., colorings, flavorings, preservatives
  - **Other components**
    e.g., DEHP, latex

Pertinent Medication Factors

- **Pharmacology**
- **Pharmacokinetics (LADME)**
- **Pharmacodynamics**
- **Adverse effect profiles**
- **Interactions**
  - **drug-drug**
  - **drug-nutrient**
  - **drug-lab test interference**
- **Cross-allergenicity or cross-reactivity**

ADR Information

- **Incidence and prevalence**
- **Mechanism and pathogenesis**
- **Clinical presentation and diagnosis**
- **Time course**
- **Dose relationship**
- **Reversibility**
- **Cross-reactivity/Cross-allergenicity**
- **Treatment and prognosis**

ADR Information Resources

- **Tertiary**
  - **Reference books**
    - **Medical and pharmacotherapy textbooks**
    - **Package inserts, PDR, AHFS, USPDI**
    - **Specialized ADR resources**
      - **Meyler's Side Effects of Drugs**
      - **Textbook of Adverse Drug Reactions**
    - **Drug interactions resources**
    - **Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)**
  - **Review articles**

ADR Information Resources

- **Secondary**
  - **MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)**
  - **Excerpta Medica's Embase**
  - **International Pharmaceutical Abstracts**
  - **Current Contents**
  - **Biological Abstracts (Biosis)**
  - **Science Citation Index**
  - **Clin-Alert and Reactions**

ADR Information Resources

- **Primary**
  - **Spontaneous reports or unpublished data**
    - **FDA**
    - **Manufacturer**
  - **Anecdotal and descriptive reports**
    - **Case reports, case series**
  - **Observational studies**
    - **Case-control, cross-sectional, cohort**
  - **Experimental and other studies**
    - **Clinical trials**
    - **Meta-analyses**

Causality Assessment

- **Prior reports of reaction**
- **Temporal relationship**
- **De-challenge**
- **Re-challenge**
- **Dose-response relationship**
- **Alternative etiologies**
- **Objective confirmation**
- **Past history of reaction to same or similar medication**

Causality Assessment

- **Examples of causality algorithms**
  - **Kramer**
  - **Naranjo and Jones**
- **Causality outcomes**
  - **Highly probable**
  - **Probable**
  - **Possible**
  - **Doubtful**

Naranjo ADR Probability Scale

This is a copy of the Naranjo ADR Probably Scale Questionnaire which is used to access an adverse drug reaction by completing the questionnaire and giving the appropriate score.

Total Score	ADR Probability Classification
9	Highly probably
5-8	Probable
1-4	Possible
0	Doubtful

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

Management Options

- **Discontinue the offending agent if:**
  - **it can be safely stopped**
  - **the event is life-threatening or intolerable**
  - **there is a reasonable alternative**
  - **continuing the medication will further exacerbate the patient's condition**
- **Continue the medication (modified as needed) if:**
  - **it is medically necessary**
  - **there is no reasonable alternative**
  - **the problem is mild and will resolve with time**

Management Options

- **Discontinue non-essential medications**
- **Administer appropriate treatment**
  e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon
- **Provide supportive or palliative care**
  e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
- **Consider rechallenge or desensitization**

Follow-up and Re-evaluation

- **Patient's progress**
- **Course of event**
- **Delayed reactions**
- **Response to treatment**
- **Specific monitoring parameters**

Reporting ADRs

Reportable

- **All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related**

Reporting ADRs

Reportable

- **Hypersensitivity**
- **Life-threatening**
- **Cause disability**
- **Idiosyncratic**
- **Secondary to Drug interactions**
  - **Unexpected detrimental effect**
  - **Drug intolerance**
  - **Any ADR with investigational drug**

Documentation and Reporting

- **Medical record**
  - **Description**
  - **Management**
  - **Outcome**
- **Reporting responsibility**
  - **JCAHO-mandated reporting programs**
  - **Food and Drug Administration**
    post-marketing surveillance
    particular interest in serious reactions involving new chemical entities
  - **Pharmaceutical manufacturers**
  - **Publishing in the medical literature**

Components of an ADR Report

- **Product name and manufacturer**
- **Patient demographics**
- **Description of adverse event and outcome**
- **Date of onset**
- **Drug start and stop dates/times**
- **Dose, frequency, and method**
- **Relevant lab test results or other objective evidence**
- **De-challenge and re-challenge information**
- **Confounding variables**

MEDWATCH 3500A Reporting Form

This is the FDA Medical Products Reporting Program

For use by user-facilities, distributors and manufacturers for MANDATORY reporting.

https://www.accessdata. fda.gov/scripts/medwatch

ISMP – QuarterWatch™ 2010
Quarter 2

- **Analyzed computer excerpts from 33,068 reports**
- **Continued increase in reports – up 12% compared to Q2 2009**
- **Reports from manufacturers increased 24%**
- **Reports from consumers and health care professionals were 25% fewer**

ISMP – QuarterWatch™ 2010
Quarter 2

FDA Drug Safety Communications

- **FDA provides easy access to important drug safety information**
- **Risk of Progressive Multifocal Leukoencephalopathy (PML) with the use of Tysabri (natalizumab)**
  - **31 confirmed cases of PML received by the FDA as of January 21, 2010**
  - **Additional information for patients and prescribers provided on website**
  - **This information will be included on the drug label and patient *Medication Guide***
  - **Limited distribution prescribing system is in place**

Risk Evaluation and Mitigation Strategy (REMS)

- **Risk management plan that utilizes strategies that go beyond professional labeling to ensure drug benefits outweigh risks**
- **The FDA Amendments Act of 2007 (FDAAA) granted the FDA the authority to require the submission and implementation of a REMS**
- **REMS are designed to meet specific serious risk mitigation goals**

REMS Considerations

- **Does the product fill a significant unmet need**
- **What is the magnitude of the risk**
- **Do the data suggest ways to mitigate the risk?**

REMS Components

- **Medication Guide for patients**
- **Communication Plan for healthcare professionals**
- **Elements to Assure Safe Use**
- **Implementation system**

Medication Guide Requirement

- **Patient labeling could help prevent serious adverse events**
- **The product has serious risks that could affect a patient's decision**
- **Patient adherence to directions is crucial to product effectiveness**

Communication Plan

- **If FDA determines a communication plan is needed, it can include:**
  - **Letters to healthcare providers**
  - **Disseminating information through professional societies about serious risk of the drug and any elements to assure safe use**

Elements to Assure Safe Use

- **Prescriber training or certification**
- **Certification of dispensers**
- **Drug administration limited to certain health care settings**
- **Documentation of safe use prior to dispensing**
- **Required monitoring of patients**
- **Enrollment of patients in a registry**

REMS Example
Victoza® (Liraglutide)

- **Goal is to inform providers of the risk of acute pancreatitis (including necrotizing pancreatitis) and potential risk of medullary thyroid carcinoma**
- **Medication guide will be dispensed with each prescription**
- **Communication Plan**
  - **Dear doctor letter**
  - **Direct mail letter each year x 3 yrs**
  - **Highlighted information for prescribers will be distributed by manufacturer representatives**

Sample of Victoza® Medication Guide

- Before taking Victoza, tell your healthcare provider if you have had:
- **pancreatitis**
- **stones in your gallbladder (gallstones)**
- **a history of alcoholism**
- **high blood triglyceride levels**
  - **These medical conditions can make you more likely to get pancreatitis in general. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking Victoza.**
- While taking Victoza:
- **Stop taking Victoza and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.**

How to get FDA Drug Safety Alerts

- **FDA Drug Safety Newsletter**
  - **http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/default.htm**
- **MedWatch Safety Alerts**
  - **http://www.fda.gov/Safety/MedWatch/ucm168422.htm**
- **FDA Patient Safety News**
  - **Video news show for health professionals**
  - **http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/index.cfm**

Future

- **I-phone apps for MedWatch**
- **Hospital systems to report adrs directly to FDA**
- **FAERS – FDA Adverse Event Reporting System (enhanced analysis)**
- **Standardization of reporting to include data form Japan and Europe**
- **Federal Adverse Event Task Force (FAET)**
- **Innovative ways to increase reporting and identification of adverse drug reactions**

- **Slone Epidemiology Center at Boston University. Patterns of medication use in the United States, 2006. [PDF - 141 KB]**
- **Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006;296:1858-66.**
- **Institute of Medicine. Committee on Identifying and Preventing Medication Errors. Preventing Medication Errors, Washington, DC: The National Academies Press 2006.**