

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**

Definition - WHO

– WHO

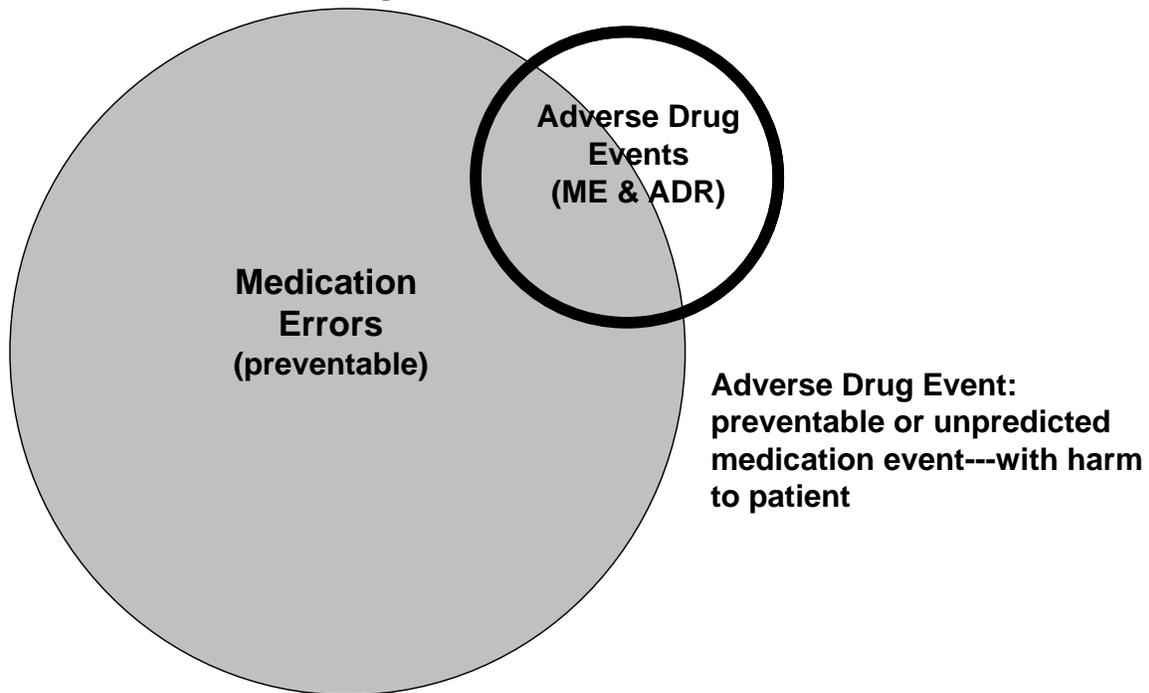
- response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function
- Purposely excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

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.



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.**

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

Classification

- **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:**
 - **Provoking 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 medication 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

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

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

	Yes	No	Do Not Know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	___
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	___
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	___
4. Did the adverse reactions appear when the drug was readministered?	+2	-1	0	___
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	___
6. Did the reaction reappear when a placebo was given?	-1	+1	0	___
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	___
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	___
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	___
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	___
			Total Score	___

Total Score ADR Probability Classification

9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

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

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

Form Approved OMB No. 0910-0281 Expires 04/30/03
See OMB statement on reverse

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

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

Page ____ of ____

MED report # _____
OF this report # _____
FDA Use Only

A. Patient information			
1. Patient identifier	2. Age at time of event: or Date of birth:	3. Sex <input type="checkbox"/> female or <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
B. Adverse event or product problem			
1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)			
2. Outcomes attributed to adverse event (check all that apply):			
<input type="checkbox"/> death	<input type="checkbox"/> life-threatening	<input type="checkbox"/> hospitalization – initial or prolonged	<input type="checkbox"/> disability
			<input type="checkbox"/> congenital anomaly
			<input type="checkbox"/> required intervention to prevent permanent impairment/damage
			<input type="checkbox"/> other: _____
3. Date of event (month/year)	4. Date of this report (month/year)		
5. Describe event or problem			
6. Relevant tests/laboratory data, including dates			
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepato/renal dysfunction, etc.)			
C. Suspect medication(s)			
1. Name (give labeled strength & manufacturer, if known)			
#1 _____			
#2 _____			
2. Dose, frequency & route used		3. Therapy dates (if unknown, give duration) <small>(month/year to month/year)</small>	
#1 _____		#1 _____	
#2 _____		#2 _____	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced	
#1 _____		#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
#2 _____		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
6. Lot # (if known)		7. Exp. date (if known)	
#1 _____		#1 _____	
#2 _____		#2 _____	
9. NDC # – for product problems only (if known)			
#1 _____			
#2 _____			
10. Concomitant medical products and therapy dates (exclude treatment of event)			
D. Suspect medical device			
1. Brand name			
2. Type of device			
3. Manufacturer name & address			4. Operator of device
			<input type="checkbox"/> health professional
			<input type="checkbox"/> lay user/patient
			<input type="checkbox"/> other: _____
6. model # (month/year)			5. Expiration date (month/year)
catalog #			7. If implanted, give date (month/year)
serial #			8. If explanted, give date (month/year)
lot #			9. Device available for evaluation? (Do not send to FDA)
other #			<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> returned to manufacturer on _____ (month/year)
10. Concomitant medical products and therapy dates (exclude treatment of event)			
E. Initial reporter			
1. Name & address			phone # _____
2. Health professional? <input type="checkbox"/> yes <input type="checkbox"/> no			
3. Occupation			
4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unknown			

PLEASE TYPE OR USE BLACK INK

FDA
FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

ISMP – QuarterWatch™ 2008

- Fatal, disabling and serious ADEs reported to FDA increased by 25% in 2008 compared to 2007**
- 2008 FDA reports of 100,789 cases of severe injury vs. 80,598 in 2007**
- 15,189 patient deaths reported in 2008 vs 9,728 in 2007 (56% increase)**

ISMP – QuarterWatch™ 2008

- **Large generic drug recalls (ex. heparin vials, digoxin, morphine, propafenone tablets)**
- **Increase voluntary reporting by healthcare providers**
- **Increase reporting by manufacturers who learned of more events through patients**
- **FDA public health advisories encouraged reporting of ADRs with link to MedWatch site**

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**

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>