CLINICAL ANALYSIS OF ADVERSE DRUG REACTIONS

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Disclaimer

The views in this presentation on clinical analysis of adverse drug reactions are my own opinion and do not necessarily represent the views of the FDA

Objectives

• Define adverse drug reactions
• Discuss epidemiology, classification and causes of ADRs
• Describe basic methods to detect, assess, manage and document ADRs in the clinical setting
• Describe postmarketing drug safety surveillance, the FDA MedWatch program, and FDA Adverse Event Reporting System (FAERS)
• Discuss FDA adverse drug reaction initiatives and mitigation strategies
**Definitions**

<table>
<thead>
<tr>
<th>WHO – Adverse Drug Reaction</th>
<th>FDA – Adverse Drug Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to a drug that is <em>noxious and unintended</em> and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function.</td>
<td>Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.</td>
</tr>
</tbody>
</table>


Requirements for adverse drug reaction reporting. Geneva, Switzerland: World Health Organization; 1975

**Epidemiology**

- In 2006 an average of 82% of American adults took at least one medication, and 29% took five or more*
- In 2004 and 2005 an estimated 700,000 emergency department visits and 120,000 hospitalizations were due to ADEs annually**
- $3.5 billion is spent on extra medical costs of ADEs annually (per 2006 yr cost estimates)***


http://www.cdc.gov/MedicationSafety/basics.html


**ADEs Projected to Increase**

- 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

- Severity
- Type

Classification – Severity of Event

- Minor
- Moderate
- Serious
- Serious life-threatening
- Serious lethal

FDA Serious Adverse Drug Experience

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Result in death
- Life-threatening
- Hospitalization (new or prolonged)
- Disability or incapacity
- Congenital anomaly, birth defect
- Other: require intervention to prevent any of the above

http://www.ecfr.gov/cgi-bin/text-idx?SID=b79d08f290d0fe79d912bd82e97bd16f&node=21:5.0.1.1.4.2.1.11&rgn=div8
Classification - Type

Type A (dose related)
- extension of pharmacologic effect
- often predictable and dose dependent
- generally reversible
- e.g., propranolol and heart block, anticholinergics and dry mouth

Type B (not dose related)
- idiosyncratic or immunologic reactions
- rare and unpredictable
- e.g., chloramphenicol and aplastic anemia
- rash caused by beta lactam antibiotics

ADR Risk Factors (some examples)

- 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
- Decision Support systems
- Physician order entry, pharm info system

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

ADE Reporting in Clinical Trials

21 CFR 312.32 IND Safety Reporting

- Changes to safety information reporting during clinical trials began in March 2011 and enforcement on September 28, 2011
- Clarifies definitions (adverse event, suspected adverse reaction, unexpected adverse event)
- Suspected adverse reaction
  - Reasonable possibility the drug caused the event
- Revised requirements for expedited reporting

IND Safety Reporting Issues

- Adverse events that were likely to have been a manifestation of the underlying disease
- Adverse events that commonly occurred in the study population
- Adverse events that were study endpoints

Safety in the Lifecycle of FDA-regulated Products

- Pre-clinical
  - Safety & Biological Activity
- Phase 1
  - Safety & Dosage
- Phase 2
  - Safety & Efficacy
- Phase 3
  - Safety & Efficacy
- Post-Marketing
  - Safety Surveillance

Limitations of Premarketing Clinical Trials

- Size of the patient population studied
- Narrow population - often not providing sufficient data on special groups
- Narrow indications studied
- Short duration
ADR Assessment

Assessment Questions
- Reaction timely to medication being started (temporal association)
- Resolution timely to discontinuation of the drug (dechallenge)
- Other plausible explanations and drugs are ruled out
- Objective confirmation (laboratory test)
- Reaction reoccurs if medication re-administered (rechallenge)

Preliminary Assessment
- Fully characterize the event (signs/symptoms)
- Differential diagnosis (alternate explanations)
  - Is this an exacerbation of a pre-existing condition?
  - Laboratory error?
  - Non-drug cause?
- 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
- Onset, duration, frequency of event
- Response to treatment
- Improvement or continuation of adverse event when drug discontinued

### Pertinent Patient/Disease Factors
- **Demographics**
  - age, race, ethnicity, gender, height, weight
- **Medical history and physical exam**
  - dehydration, autoimmune condition, HIV infection, pregnancy, dialysis
  - Recent procedures or surgeries, and complications
- **End-organ function**
- **Laboratory tests and diagnostics**
- **Social history** (tobacco, alcohol, substance abuse),
- **Pertinent family history**
- **Nutritional status** (malnutrition, weight loss)

### Pertinent Medication Factors
- **Thorough medication history**
  - Prescription and non-prescription medications
  - Alternative and investigational therapies
  - Allergies, intolerances, history of medication reactions
  - Adherence to prescribed regimens
- **Characteristics of suspected drug**
  - Indication, dose, volume
  - Administration (route, schedule, duration)
- **Formulation**
  - Pharmaceutical excipients (diluent, preservatives, colorings)
  - Other components (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

Assessing ADR Risk
Review drug pharmacology, absorption, and metabolism
- Review up-to-date drug labels (package insert)
  - Drugs@FDA
- Safety Alerts – FDA and international regulatory agencies
- Published literature
  - Case reports, reviews, clinical trials
- Drug information resources
  - Livertox (NLM and NIDDK)
  - Micromedex
Evaluating a Publication for ADRs

- Are adverse events actually reported?
- Passive or active surveillance used to identify AE?
- Is a validated checklist available?
- Are pre-specified objective endpoints reported?
- Are patient withdrawals because of adverse events reported?
- Are AEs reported in the abstract, methods, and results section?
- Discussion includes a balanced discussion of harms and benefits?
- Is there external validity?


Minimizing and Managing ADRS

- 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 if:
  - it is medically necessary (modified as needed)
  - 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, phytanadione, protamine, sodium polystyrene sulfonate, digoxin immune Fab (ovine), 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

Causality Assessment
- Prior reports of reaction (controlled trials, known biological mechanism, drug class effect, etc.)
- Temporal relationship
- Dechallenge
- Rechallenge
- Dose-response relationship
- Alternative etiologies
- Objective confirmation
- Past history of reaction to same or similar medication

Causality Assessment Tools
- Examples of causality algorithms
  - Naranjo Adverse Drug Reaction Probability scale
  - World Health Organization, the Uppsala Monitoring Centre (WHO-UMC) causality assessment system (http://who-umc.org/Graphics/24734.pdf)
- Causality outcomes
  - Naranjo: definite, probable, possible, doubtful
  - WHO-UPR: certain, probable, possible, unlikely, unclassified, unassessable
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
- Dechallenge and rechallenge information
- Confounding variables

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

Naranjo ADR Probability Scale for Case Example

<table>
<thead>
<tr>
<th>Total Score</th>
<th>ADR Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Definite</td>
</tr>
<tr>
<td>5-8</td>
<td>Probable</td>
</tr>
<tr>
<td>1-4</td>
<td>Possible</td>
</tr>
<tr>
<td>0</td>
<td>Doubtful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case Example</th>
<th>Yes</th>
<th>No</th>
<th>Do/Did Not Happen</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>3. Did the adverse event improve when the drug was stopped?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>4. Did the adverse event improve when the drug was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>5. Are there alternative causes other than the drug that could have caused the reaction?</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>6. Did the reaction occur when a placebo was given?</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>7. Is the reaction consistent with the known adverse effects of the drug?</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>8. Was the reaction seen when the dose was increased or decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same drug in a previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
</tbody>
</table>

Total Score: 8
Postmarket Adverse Event Reporting and FDA MedWatch

Benefits of Postmarketing Monitoring

The ability to study the following:

• Low frequency reactions (not identified in clinical trials)
• High risk groups
• Long-term effects
• Drug-drug/food interactions
• Increased severity and/or reporting frequency of known reactions

Types of Postmarketing Surveillance

• Spontaneous/voluntary reporting of cases
  - National (FDA MedWatch)
  - Local or Regional (Joint Commission Requirement)
  - Scientific literature publications
• Postmarketing studies (voluntary or required)
  - Observational studies (including automated healthcare databases)
    • Randomized clinical trials
• Active surveillance
  - Drug-Induced Liver Injury Network (DILIN)
  - Sentinel initiative
  - Patient registries
  - Required AE reporting (enhanced pharmacovigilance, Risk Evaluation and Mitigation Strategy requirements, etc.)
How to Report:
- Online (www.fda.gov/medwatch)
- Download the form
- Mail
- Fax 1–800–332–0178
- For questions about the form:
  - 1–800–332–1088

Consumer MedWatch Form
- MedWatch Form 3500B
- Includes 4 primary components
  - Patient
  - Product
  - Event
  - Reporter
- User-friendly format for non-health care professionals
Components of a Good Postmarketing Report

- Description of adverse event
- Identified reporter
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005

How Postmarketing Reports Get to FDA

![Diagram showing how postmarketing reports get to FDA]

Patients, consumer, and healthcare professionals

- Voluntary
- FDA MedWatch

Manufacturer

- Regulatory Requirements
- FDA

FDA Adverse Event Reporting System

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 11 million reports since 1969
- More than 1.6 million reports entered in 2015

FDA Adverse Event Reporting System (FAERS)
Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

Goal: promote safe use of drugs

*The Importance of Pharmacovigilance, World Health Organization 2002*
Divisions of Pharmacovigilance

- Evaluate the safety of drug and biologic products
- Advance public health by detecting and analyzing safety signals from all available data sources, utilizing evidence-based methods
- Recommend appropriate regulatory actions, including labeling changes, Risk Evaluation and Mitigation Strategies (REMS), to ensure safe use
- Communicate related safety information

What is a Safety Signal?

- WHO defines a signal as:
  - Reported information on a possible causal relationship between an adverse event and a drug
  - The relationship being previously unknown or incompletely documented
  - Usually requires more than one report, depending on the seriousness of the event and the quality of the information

Safety Signal Illustrations

- New unlabeled adverse events
- An observed increase in a labeled event OR a greater severity or specificity
- Unrecognized drug-drug interaction
- Newly identified at-risk population
Evaluation

Drug-Event Association

- Temporal association
- Biologic plausibility
- Dechallenge
- Rechallenge
- Alternate causes ruled out (medications and diseases)
- Prior reports of event
- Objective evidence

Characterize

- Look for trends
- Identify risk factors or at risk groups
- Dose relationship
- Drug-interaction

Regulatory Actions

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 Components

- A REMS can include
  - Medication Guide or Patient Package Insert
  - Communication Plan for healthcare professionals (HCPs)
  - Elements to Assure Safe Use (previously known as “restricted distribution”)
  - Implementation system
- Must include a timetable for assessment of the REMS (for NDAs and BLAs)

Medication Guide

- Provides FDA approved patient-friendly labeling
- Can be required if FDA determines one or more:
  - Patient labeling could help prevent serious adverse events
  - The product has serious risks that could affect patient’s decision to use or continue to use
  - Patient adherence to directions is crucial to product effectiveness

Communication Plan

- FDA approved materials used to aid sponsor’s implementation of REMS and/or inform healthcare providers about serious risks (not patient directed)
- Communication plan may include:
  - “Dear Healthcare Professional” letters
  - Dissemination of information to HCPs through professional societies
  - Information about the REMS to encourage implementation
- Specific tools used:
  - Dear Healthcare Professional Letters
  - Informational brochures, slide deck
  - Information pieces placed in professional journals or made available at scientific meetings
  - Training materials, videos
Elements to Assure Safe Use
- Certification and specialized training of HCPs who prescribe the drugs
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug in limited settings e.g., hospitals
- Drug is dispensed/administered only with evidence of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Enrollment of treated patients in registries

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 distributed to each patient when drug dispensed
- Communication Plan
  - Dear doctor letter
  - Highlighted information for prescribers will be distributed by manufacturer representatives
  - A link from Victoza website taking HCP to these documents

Sample Medication Guide Information for Victoza®
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 be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.
- For a list of Medication guides: http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm
FDA Communicates Safety Issues to the Public, Healthcare Providers and Internationally

- MedWatch Safety Alerts
- FDA Drug Safety Communications
- FDA Drug Safety Podcasts
- Postmarket Drug and Biologic Safety Evaluations (FDAAA 915) - results posted on FDA website
- Potential Signals of Serious Risks/New Safety Information Identified from FAERS (FDAAA 921) – posted quarterly
- Published literature and scientific meetings
- Video and teleconferences with foreign regulatory agencies:
  - European Medicines Agency, Canada, Australia, New Zealand
How to get FDA Drug Safety Alerts

- MedWatch Safety Alert E-Mail Updates  
  http://www.fda.gov/Safety/MedWatch/ucm168422.htm

- MedWatch safety information and reporting:  
  http://www.fda.gov/Safety/MedWatch/default.htm