Clinical Analysis of Adverse Drug Reactions

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Objectives

- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs – discussed in previous lecture
- Describe basic methods to detect, evaluate, and document ADRs
- FDA changes for ADR detection
- FDA adverse drug reaction initiatives
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.

Medication Errors (preventable)

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
Classification

- Onset
- Severity
- Type
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

- Minor
- Moderate
- Serious
- Serious life-threatening
- Serious lethal
Classification - Severity

- FDA Defines Serious ADE
  - 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

*Federal Register - Code of Federal Regulations. 21 CFR 314.80 (a) 2012*
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
Common Causes of ADRs

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

*account for 69% of fatal ADRs
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
- **Subjective report**
  - patient complaint

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

- exposure limited to few individuals
  - rare and unusual ADRs not detected
- 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
- 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, Adverse Reaction)

- Suspected adverse reaction
  - Evidence suggesting a relationship with the study drug

- 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
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)
- **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
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
Examples of causality algorithms
- Kramer
- Naranjo and Jones

Causality outcomes
- Definite
- Probable
- Possible
- Doubtful
**Naranjo ADR Probability Scale**

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

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

<table>
<thead>
<tr>
<th>Total Score</th>
<th>ADR Probability Classification</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>
Assessing ADR Risk

- Review drug labels
  • DailyMed, Drugs@FDA
- Safety Alerts – FDA, international
- Published literature (case reports, reviews, clinical trials)
- Drug information resources
  • NLM – Livertox
  • 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 AE 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 (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**

The FDA Safety Information and Adverse Event Reporting Program

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**For VOLUNTARY reporting of adverse events, product problems and product use errors.**

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### A. PATIENT INFORMATION
- **Patient Identifying Information:**
  - Name:
  - Date of Birth:
  - Sex:
  - Age:
  - Weight:
  - Other:

### B. INCIDENT EVENT / PRODUCT PROBLEM DETAIL

- **Check off any:**
  - Adverse Event
  - Product Problem (e.g., incorrect labeling)
  - Product Use Error
  - Problems with Different Manufacturer of Same Medicine
  - Other

- **Suspect Adverse Event:**
  - Illness:
  - Hospitalization - initial or prolonged
  - Other Serious (if important medical event)

- **Detailed Description of Incident:**
  - Date of Event:
  - Date of this Report:

### C. PRODUCT USE ERROR

- **Describe Event, Product or Product Use Error:**

### D. SUSPECT PRODUCT

- **Name, Strength, Manufacturer (if product label):**

### E. SUSPECT MEDICAL DEVICE

- **Brand Name:**
  - Generic Name:
  - Manufacturer Name, City and State:

### F. OTHER (CONCURRENT) MEDICAL PRODUCTS

- **Product names and dosage forms (no product use errors):**

### G. REPORTER (See confidentiality section on back)

- **Telephone:**
- **E-mail:**

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**FORM FDA 3500 (10/05)**

Substitution of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.
MedWatch Direct Reports

- Reports submitted directly to FDA through MedWatch by
  - Internet – on line reporting form
  - Mail or Fax
  - Telephone 1-800-FDA-1088
Post-marketing Adverse Events

Patients, consumer and healthcare professionals

FDA MedWatch

FDA’s Adverse Event Reporting System database

Manufacturer

FDA
FAERS

- FAERS (FDA Adverse Event Reporting System) database for drugs and biologics
  - Adverse event reports
  - Medication error reports
- Replaced AERS on September 10, 2012.
- FDA will use FAERS for regulatory compliance, and to monitor for adverse events and medication errors that might occur with CDER and CBER regulated products.
Reports Received and Reports Entered into AERS by Year
Reports Received and Reports Entered into FAERS/AERS by Year

Reports Entered into FAERS

- PERIODIC
- 15-DAY
- DIRECT

Year

Number of Reports

0 100000 200000 300000 400000 500000 600000 700000 800000 900000 1000000

Division 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, REMS, etc.
- Communicate related safety information
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) and increases with number of infusions
  - 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

- Communication Plan for healthcare professionals
- Elements to Assure Safe Use (previously “restricted distribution”)
- 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
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.

- For a list of Medication guides:
  http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm
How to get FDA Drug Safety Alerts

- FDA Drug Safety Newsletter

- MedWatch Safety Alerts
  - [http://www.fda.gov/Safety/MedWatch/ucm168422.htm](http://www.fda.gov/Safety/MedWatch/ucm168422.htm)

- FDA Patient Safety News
  - Video news show for health professionals

- MedWatch reporting:
  - [http://www.fda.gov/Safety/MedWatch/ucm335923.htm](http://www.fda.gov/Safety/MedWatch/ucm335923.htm)
Questions ???