Adverse Drug Reactions: A Perspective

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Global Medical Affairs
Wyeth Pharmaceuticals
Presentation Outline

- From the Headlines!
- What is an adverse drug reaction (ADR)
- Types and Classification of ADRs
- Risk Factors for ADRs and Examples
- Regulations and the FDA: History, Background, and Postmarketing Surveillance
- Specific ADR Cases
- Future/Conclusions
From The Headlines!!

The New York Times

Vioxx™ Recall May

Los Angeles Times

Report: ....... Held Back on Drug Dangers
From The Headlines!!

FDA Officer Suggests Strict Curbs on 5 Drugs
Makers Dispute Claims About Health Risks
The Perceptions and Implications

- Adverse drug reactions have had significant media exposure, with the resulting impact on the public at large.
- Pharmaceutical companies have felt the pinch of mismanagement of high-profile ADR reports that have effected the industry.
- Patient care may suffer or they may lose confidence in a drug (especially in the case of recall).
The Reports and Findings

- A meta-analysis of 39 studies found an in-hospital incidence of ADRs of 6.7%, and an incidence of fatal ADRs of 0.3%.
- This makes fatal ADRs amongst the top six leading causes of death in the United States.
- 30% to 60% are preventable.
- ADRs may lead to an additional $1.56 to $4 billion in direct hospital costs per year in the United States.

Adverse Drug Reactions: What are they?

- An injury resulting from medical intervention related to a drug

- Any noxious and unintended effect of drug that occurs at doses used in human for prophylaxis, diagnosis, or treatment
  - WHO definition

- Excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

- Majority of ADRs are caused by predictable, nonimmunologic effects (75 to 80 percent)

Reference: http://www.safetyandquality.org/definition/adversedruevent.htm
Relationship Between ADEs and ADRs

Adverse Drug Reactions

Adverse Drug Events

Potential Adverse Drug Events
Trivial Medication Errors

Not Preventable
Inherent Risk of Drug

Preventable Medication Errors

Adapted From: http://www.annals.org/cgi/content/full/142/1/77
Adverse Drug Reactions: How do we learn about them?

- Most common adverse reactions are detected in premarketing clinical trials (reported in prescribing information)
- However, most clinical trials are of short duration, and patient numbers in trials are low compared to population
  - Latent ADRs often missed
  - 3000 patients at risk needed to detect with an incidence rate of 1/1000 with 95% certainty
- Most trials also exclude the very young and old, pregnant women, patients with multiple diseases, and any potentially interacting medications
- Additional ADRs are discovered once a drug enters the marketplace

## Types of Drug Reactions: Nonimmunologic

<table>
<thead>
<tr>
<th>Nonimmunologic</th>
<th>Predictable</th>
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<tbody>
<tr>
<td></td>
<td>Pharmacologic side effect</td>
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<tr>
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<td>Secondary pharmacologic side effect</td>
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<tr>
<td></td>
<td>Drug toxicity</td>
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<td>Drug-drug interactions</td>
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<td>Drug overdose</td>
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<td></td>
<td>Unpredictable</td>
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<tr>
<td></td>
<td>Pseudoallergic</td>
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<td>Idiosyncratic</td>
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<td>Intolerance</td>
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<td>Dry mouth from antihistamines</td>
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<td>Thrush while taking antibiotics</td>
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<td>Hepatotoxicity from methotrexate</td>
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<td>Seizure from theophylline while taking erythromycin</td>
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<td>Seizure from excessive lidocaine (Xylocaine)</td>
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<td></td>
<td>Anaphylactoid reaction after radiocontrast media</td>
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<td></td>
<td>Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy</td>
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<tr>
<td></td>
<td>Tinnitus after a single, small dose of aspirin</td>
</tr>
</tbody>
</table>

G6PD = glucose-6-phosphate dehydrogenase.

Adapted From: [http://www.aafp.org/afp/20031101/1781.html](http://www.aafp.org/afp/20031101/1781.html)
# Types of Drug Reactions: Immunologic

<table>
<thead>
<tr>
<th>Type I reaction (IgE-mediated)</th>
<th>Anaphylaxis from b-lactam antibiotic</th>
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<tr>
<td>Type II reaction (cytotoxic)</td>
<td>Hemolytic anemia from penicillin</td>
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<tr>
<td>Type III reaction (immune complex)</td>
<td>Serum sickness from anti-thymocyte globulin</td>
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<tr>
<td>Type IV reaction (delayed, cell-mediated)</td>
<td>Contact dermatitis from topical antihistamine</td>
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<tr>
<td>Specific T-cell activation</td>
<td>Morbilliform rash from sulfonamides</td>
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<tr>
<td>Fas/Fas ligand-induced apoptosis</td>
<td>Stevens-Johnson syndrome</td>
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<tr>
<td></td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Other</td>
<td>Drug-induced, lupus-like syndrome</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant hypersensitivity syndrome</td>
</tr>
</tbody>
</table>

Adapted From: [http://www.aafp.org/afp/20031101/1781.html](http://www.aafp.org/afp/20031101/1781.html)
ADRs by Drug Class

Adapted From: http://www.vh.org/adult/provider/pharmacyservices/PTNews/2003/may.html
Body Systems Commonly Involved

- Central Nervous System
- Hematologic
- Cardiovascular
- Renal/Genitourinary
- Sensory
  - Neuropathy
  - Auditory
- Dermatologic
  - especially visible lesions or eruptions
- Gastrointestinal
- Metabolic
ADR Effects (Erythema Multiforme)

Used with permission from Michelle Ehrlich, MD and eMedicine.com, Inc., 2005
ADR Effects (Gingival Enlargement due to Ca\(^{2+}\)-Channel Blockers)

Used with permission from Carl Allen, DDS and eMedicine.com, Inc., 2005
ADR Effects (Coumadin Necrosis of the Leg)

Used with permission from Michelle Ehrlich, MD and eMedicine.com, Inc., 2005
Risk Factors for Adverse Drug Reactions

- Simultaneous use of several different drugs
  - Drug-drug interactions
- Very young, or very old in age
- Pregnancy
- Breast Feeding
- Hereditary Factors
- Disease states which may effect drug absorption, metabolism, and/or elimination

Reference: http://www.merck.com/mmhe/sec02/ch015/ch015e.html
Risk Factors Examples: Simultaneous Drug Use or Drug-Drug Interactions

- Cerivastatin-Gemfibrozil interactions in hypercholesterolemia patients (rhabdomyolysis)

- Coumadin-NSAID interactions (increased inhibition of platelet aggregation)

- Venlafaxine-indinavir interactions in depressed HIV-infected patients (decreased indinavir concentrations)

References:
- Psaty BM, et al, JAMA, 2004 Dec 1; 292 (21), 2622-31
Risk Factors Examples: Age Related Issues

- Children are often at risk because their capacity to metabolize drugs is usually not fully developed
  - Newborns cannot metabolize or eliminate chloramphenicol, an antibiotic
  - Children younger than 18 may be at risk of developing Reye’s syndrome if given acetylsalicylic acid (aspirin) while infected with chickenpox or influenza
  - Central nervous system effects of topiramate in children (seizures, tremor, and dizziness)

References:
http://www.merck.com/mmhe/sec02/ch015/ch015e.html
Shechter T, et al, Pharmacoepidemiol Drug Saf. 2004 Nov 1
Risk Factors Examples: Age Related Issues

- ADRs, including drug interactions, are a common cause of admission to hospitals in the elderly
- Reasons for ADRs in the elderly:
  - Concomitant use of several medications
  - Disease states leading to drug ADME changes
  - Decreased drug ADME activity due to age
- These conditions are exacerbated by malnutrition and dehydration, common in the elderly

Risk Factors Examples: Pregnancy

- Use of sulfonamides (antibiotic) can lead to jaundice and brain damage in the fetus
- Warfarin use for anticoagulation can lead to birth defects, and increased risk of bleeding problems in newborns and mothers
- Lithium, for bipolar disorder, can lead to defects of the heart, lethargy, reduced muscle tone, and underactivity of the thyroid gland.

Reference: http://www.merck.com/mmhe/sec22/ch259/ch259a.html#tb259_1
Risk Factors Examples: Breastfeeding

- Similar concerns, as for other children with underdeveloped capability to metabolize or excrete xenobiotics
- Many drugs can be passed from mother to infant via breast milk
  - Amantadine (antiviral)
  - Cyclophosphamide (antineoplastic)
  - Cocaine (Schedule 2 FDA drug)
  - Carisoprodol (skeletal muscle relaxant)

Risk Factors Examples: Hereditary Factors

- Genetic polymorphisms may play a role
  - Evident in CYP2C9 and 2C19, especially in the Asian population (phenytoin)
  - May lead to impaired metabolism in mutation of enzymes

- Higher risk of hemolysis in some populations, such as African, Middle Eastern, and South East Asian races
  - Quinolones
  - Antimalarials

Reference: [http://www.cppe.man.ac.uk/openlearning/e_adr/section2.asp](http://www.cppe.man.ac.uk/openlearning/e_adr/section2.asp)
Risk Factors Examples: Disease States

- Metabolism (Phase I or II) may be impaired with hepatic disease
  - Cirrhosis
  - Hepatic Carcinoma

- Renal Insufficiency
  - Acute or Chronic Renal Failure
  - Decreased glomerular filtration rate (GFR)

- Drug levels may become toxic if too high, so dosing modifications may be indicated

Regulations and the FDA: History, Background and Postmarketing Surveillance
FDA Historical Milestones

1906  Food and Drugs Act is Passed.
Signed by President Theodore Roosevelt.

1938  It prohibits interstate commerce in misbranded & adulterated foods, drinks, and drugs.

1951

1962

1968

The Federal Food, Drug, and Cosmetic (FDC) Act is passed.

Passed by Congress.

Many provisions, one of which required manufacturer prove the safety of a drug before it can be marketed.

FDA Historical Milestones

1906  1938  1951  1962  1968

Durham-Humphrey Amendment

Defined prescription drugs as those unsafe for self-medication and which should be used only under a doctor’s supervision

FDA Historical Milestones

1906  1938  1951  1962  1968

- Thalidomide
- Kefauver-Harris Drug Amendments
- Consumer Bill of Rights

Drug manufacturers were required to prove to FDA the safety and effectiveness of their products before marketing them.

Consumer Bill of Rights (informed consent)

FDA Historical Milestones

1906 1938 1951 1962 1968

Reorganization of federal health programs.
Places FDA in the Public Health Service.

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The Role of the FDA

- Responsible not only for drug approval, but for monitoring drug safety after they reach the market
  - Pharma companies report ADEs to FDA in the NDA or aNDA (data from clinical trials)
- FDA’s Office of Drug Safety carries out this role
  - Adverse Event Reporting System (AERS)
- AERS receives reports from two sources:
  - Mandatory reports from Pharma companies
  - Adverse event reports from HCPs

FDA Adverse Event Reporting System

http://www.fda.gov/cder/aers/default.htm
**The Role of the FDA and the AERS**

- Majority of reports come from pharma companies
- Late or non-reporting of ADRs are major problems
  - Benoxaprofen (Oraflex)
  - Ticrynafen (Selacryn)
  - Nomifensine (Merital)
- Criminal prosecutions have occurred
- Warning letters can be sent in some cases of late reporting of ADEs

Labeling Changes due to Post-Marketing Surveillance

- Many requested label changes have occurred due to adverse drug events *post-marketing*
  - Many companies proactively update drug labels based on information received in the postmarketing setting

- **Examples:**
  - Protease Inhibitors – Increases in blood sugar levels in HIV patients
  - Loratadine/pseudoephedrine – Upper GI tract narrowing and decreased esophageal peristalsis

- **Black Box Warnings now used for products with potential for life-threatening ADRs**
  - Letters go out to physicians, and close monitoring is called for

Serzone is an antidepressant

Patients were at an increased risk of liver failure and/or toxicities

Serzone no longer manufactured or marketed in the U.S.

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE.

The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 – 300,000 patient-years of SERZONE treatment. The total patient-years is a summation of each patient’s duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS).

Ordinarily, treatment with SERZONE should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however baseline abnormalities can complicate patient monitoring.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS: Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels ≥ 3 times the upper limit of NORMAL, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.
Specific ADR Cases
Mibefradil (Posicor™)

- **Indication**: Ca$^{2+}$-channel blocker for hypertension

- **ADR Problem**: Potent *inhibitor* of CYP3A4
  - Drug-drug interactions noted in patients

- **Withdrawn**: Posicor™ withdrawn from market in June 1998

Ahmad S.R., J Gen Intern Med, 2003; 18:57-60
Troglitazone (Rezulin™)

- **Indication**: Antidiabetic agent used in combination with insulin or sulfonylurea for Type II diabetes

- **ADR Problem**: Hepatotoxicity
  - Indicated by increased liver transaminase levels
  - Some cases of liver transplantation, and a few deaths reported

- **Withdrawn**: Rezulin™ recalled from market in 2000

References: [http://www.fda.gov/bbs/topics/ANSWERS/ANS00831.html](http://www.fda.gov/bbs/topics/ANSWERS/ANS00831.html)
Ahmad S.R., J Gen Intern Med, 2003; 18:57-60
Grepafloxacin (Raxar™)

- **Indication**: Oral fluoroquinolone antibiotic

- **ADR Problem**: Linked to prolongation of the heart’s QT interval, leading to ventricular arrhythmia

- **Withdrawn**: Raxar™ removed from the market in 1999

References:
- [http://www.who.int/medicines/organization/qsm/activities/drugsafety/orgqsmalerts.shtml](http://www.who.int/medicines/organization/qsm/activities/drugsafety/orgqsmalerts.shtml)
Cerivastatin (Baycol™)

- **Indication**: Oral statin to lower cholesterol

- **ADR Problem**: Rhabdomyolysis (injury to skeletal muscle)
  - Muscle weakness and myalgia very common
  - Many cases seen in combination with gemfibrazil
  - Deaths reported with cerivastatin, although no definitive link

- **Withdrawn**: Baycol™ removed from the market in 2001

References: Psaty BM, et al, JAMA, 2004 Dec 1; 292 (21), 2622-31
Ahmad S.R., J Gen Intern Med, 2003; 18:57-60
Conclusions/Future

- Adverse drug reactions have implications not only for the patient, but for the entire health care system.
- Reporting of ADRs and ADEs provides clinicians and health care companies valuable insight into the toxicity profile of an agent.
- Many ADRs and ADEs are preventable, although some effects cannot be avoided (e.g. nausea in chemo treatment for cancer).
- Better research and greater understanding of disease processes will lead to more effective, and hopefully, safer drug products.
Questions??