Spontaneous Reporting

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- The views expressed do not necessarily represent those of the Agency or the United States

Outline

- Adverse Drug Reactions
  - Definition
  - Classification
  - Magnitude
- Spontaneous Reporting
  - Definition
  - Goals
  - Strengths
  - Limitations
  - Reporting related issues
- Analysis
  - Qualitative
  - Quantitative
- Conclusions

Notable Quote

- If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes.

Oliver Wendell Holmes
Medical Essays, Currents & Counter-Currents in Medical Science, 1861

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Adverse Drug Reaction (ADR): WHO Definition

- Any noxious, unintended, and undesired effect of a drug, at doses used in humans for prophylaxis, diagnosis, or therapy
- Excludes intentional and accidental poisoning (ie. overdose), drug abuse, errors in drug administration or noncompliance

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Adverse Drug Reaction (ADR): FDA Definition

- 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 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; any failure of expected pharmacological action

-21 CFR 314.80
-21 CFR 310.305

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Classification of ADRs

- Type A
- Type B
- Type C
- Type D

Rawlins and Thompson, 1977
Grahame-Smith and Aronson. 1992

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'Type A' ADRs

- Exaggeration of the desired therapeutic effect
- Uncommon at normal dose
- Dose-related

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'Type B' ADRs

- Unpredictable
- Bizarre
- Sudden and dramatic onset

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'Type C' ADRs

- Long-term drug effects including:

  - adaptive changes (drug tolerance)

  OR

  - withdrawal (rebound) effects

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'Type D' ADRs

- Delayed reactions including:

  - carcinogenesis

  OR

  - effects associated with reproduction

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Magnitude of the Problem

- ADRs responsible for approximately 1.5 million hospitalizations a year (4K/day)
- About 770,000 patients experience ADRs while in hospital (2K/day)
- ADR may represent 4th-6th leading cause of death (ahead of pulmonary disease, accidents, pneumonia, and diabetes)
- In 1994, an estimated 106,000 hospital deaths related to ADRs

Wolfe SM, et al. Worst Pills Best Pills 2005. Lazarou J, et al. JAMA 1998

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Magnitude of the Problem - 2

- Estimated cost of drug-related morbidity and mortality - US$ 136 billion a year
- An ADR during hospitalization is associated with approximately doubling the length of stay, cost and mortality

Classen DC, et al. JAMA 1997
Johnson J, et al. Arch Intern Med 1995

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What is Pharmacovigilance?

- "all scientific and data gathering activities relating to the detection, assessment, and understanding of *adverse events*."
  - generally postmarketing (post-registration)
  - principally involves the identification and evaluation of *safety signals*
  - includes identification of adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors
  - can employ pharmacoepidemiologic studies

FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. March, 2005

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What is Spontaneous Reporting?

- The process of reporting of all unsolicited reports of adverse events from health care professionals or consumers to the FDA (or any appropriate authority) is called spontaneous reporting

"Ahmad SR, et al. Spontaneous reporting in the United States. Chapter 9. In Strom's Pharmacoepidemiology, 2005 p. 135-159.

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Why Spontaneous Reporting?

Limitations of Pre-marketing Clinical trials

- Too small --- 2,000-4,000
- Too short --- <1 yr of exposure
- Too narrow
  - excludes patients with significant co-morbidity and/or concomitant meds & special population - elderly, children, pregnant women

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Why Spontaneous Reporting? - 2

- After marketing, new information on drug safety becomes available
  - Domestic use of the product
  - Experience in other countries
- New safety information may be generated on other drugs in the same class
- Benefit-risk profile of approved drugs is continually assessed throughout the life cycle of a drug

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Spontaneous Reporting - Goals

- Identify new (less frequent) ADRs
- Detect drug safety signals or hypotheses about drug-AE associations
  - Does a risk exist?
- Identify drug-drug/food interactions
- Identify risk factors/at-risk populations for known ADRs
- Identify change in reporting of an AE over time
- Identify manufacturing problems
- Identify prescribing problems
- Reduce the risk of drug toxicity to enhance safe use

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Spontaneous Reporting - Strengths

- Potentially maintain ongoing surveillance of all patients and all drugs
- Relatively inexpensive
- Generation of hypothesis and signals
- Good for identifying rare, serious drug-induced events with low background rate

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Spontaneous Reporting - Limitations

- Passive surveillance
- Adverse event recognition
- Underreporting
- Duplicate reporting
- Report quality
  - Incomplete or limited information
- Reporting biases

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Bill Inman's 7 "Deadly Sins" of Underreporting

- Complacency
- Fear of litigation
- Guilt of causing harm
- Ambition to publish
- Ignorance
- Reluctance
- Lethargy

Factors Affecting Reporting

- Nature of the event
- Length of time drug is on the market – Weber's effect
- Publicity/Media attention
- Litigation – class action lawsuits
- Extent and quality of manufacturer's surveillance systems
- Rx or OTC status of the drug
- Reporting regulations

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Factors Affecting Reporting for OTC Drugs

- Problem of under-reporting for OTC drugs > than that for *Rx* drugs
- On Dec 22, 2006, a law was signed in the U.S. which became effective in December 2007, and requires mandatory reporting of serious AE associated with all OTC drugs
  - In July 2009, FDA issued a guidance for industry which provides guidance to industry on complying with the law
- No learned intermediary who is aware of the exposure
  - Consumers account for a large proportion of reports

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Uses of Spontaneous Reports

- Labeling purposes
- Case series
- Comparative analyses
- Signal development

Postmarketing reporting requirements – Individual case elements

Must be able to identify:

- Reporter
- Identifiable Patient
- Product
- Specific Adverse Event

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Which ADRs constitute Serious?

- Serious
  - Regulatory concept
  - *Not necessarily the same as "severe"*
  - Criteria
    - Fatal or immediately life-threatening
    - Causes persistent or significant disability or incapacity
    - Causes or prolongs inpatient hospitalization
    - Birth defect or congenital anomaly
    - Medically significant event

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Important Medical Event Examples

- Acute pancreatitis
- Allergic bronchospasm requiring intensive treatment in ER or at home
- Blood dyscrasias
- Convulsions that do not result in hospitalization
- Drug dependence or drug abuse

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Report Types - 1

- Unexpected
  - Any AE, the nature or severity of which is inconsistent with the applicable product information (Investigator's Brochure or Prescribing Information)
  - *Not the same as "medically anticipated"*

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Report Types- 2

- Periodic
  - All other reports - less than serious or already described in the label
    - Submitted quarterly for the first 3 years and then annually

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Analysis of AEs

- Signal detection and evaluation
  - Signal - Report(s) of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance.
    (CIOMS 4, 6)

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Analysis of AEs

- Qualitative
  - Case ascertainment
    - Exactly what is being reported?
    - AE dictionaries
      - MedDRA
      - COSTART
      - WHOART
  - Caused by drug?

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Evidence To Suggest A Causal Relationship

- Temporally associated with use of drug
- Biologically plausible
- No other likely causes
  - Underlying diseases or disease progression
  - Concurrent meds
- Event abates after drug is stopped (+ dechallenge)
- Event recurs when drug is restarted (+ rechallenge)

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Quantitative Analysis of AEs

- Incidence
- Reporting rate
- Observed to Expected
- Disproportionality analyses

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Incidence

- # of events/population at risk
- Best source: RCT
- Second best: cohort study
- Cannot be determined from spontaneous reports
  - Bias in spontaneous reporting (numerator)
  - Exposure uncertain (denominator)

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Reporting rate

- Reporting rate is not equal to incidence rate
- # of case reports of AE of interest/
  estimated total number of prescriptions
- Reporting rate is compared to the reporting rate of comparator drugs with similar indication
- If Reporting rate of drug of interest is > than background rate = potential association between the drug & AE

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Reporting Rate – Example - 1

- Review of case reports identified signal - pulmonary fibrosis & anti-androgen nilutamide
- Reporting rate (adjusted for market age and calendar time) for nilutamide and two other anti-androgens were calculated
- Higher Reporting rate with nilutamide → labeling change

Ahmad SR, et al. Annals of Internal Medicine, 2003

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Reporting Rate – Example 2

- Review of case reports identified signal – acute pancreatitis in association with the antidiabetic drug exenatide*
- Reporting rate for exenatide and other antidiabetics were calculated
- Higher Reporting rate with exenatide → labeling change

*Ahmad SR, Swann J. *N Engl J Med* 2008;358:1971-2.

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Observed to Expected Analysis

- Reporting rates transformed into person-time through application of typical course/length of therapy
- Observed "reporting" density compared to expected from the reference population

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Observed to Expected Analysis - 2

- Using nilutamide and pulmonary fibrosis example
- Person-time of drug exposure calculated from commercially available data
- Background rate of 'idiopathic' pulmonary fibrosis obtained from population-based epi study
- Observed to Expected analysis found that the number of reports of pulmonary fibrosis with nilutamide was 15-fold greater than expected

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Disproportionality analyses

- Data mining tool used to identify unusual or unexpected drug-event combinations
- Many algorithms
- "Denominator" derived from spontaneous reports

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What is Data Mining?

- Definition: the use of computer algorithms to analyze data in large, complex databases
- Goal: to discover patterns of associations or unexpected occurrences (i.e. "signals")
- Impact: once meaningful patterns identified, information can be evaluated for intervention as appropriate
- Important: Data mining is a tool for finding patterns…
  it cannot trump the results of individual case reviews and clinical judgment

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Disproportionality Analysis Algorithms

- Chi^2
- Proportional Reporting Ratio – S. Evans
- Bayesian confidence propagation neural network (BCPNN) – Linquist et al.
- Multi Gamma Poisson Shrinkage (MPGS) - W. DuMouchel

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Assessing Clinical Significance of ADR

- Does the ADR change the risk/benefit?
- Can risk factors be identified?
  - drug interaction, disease state, dietary factors
- Are there subgroups at risk?
  - Elderly
  - Young
  - Renal or hepatic impaired
- Can risk be managed?

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Factors Affecting Acceptability Of Risk

- Severity
- Reversibility
- Frequency
- Susceptible populations
- Alternatives available
- Abuse/misuse potential

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Regulatory Options

- Status quo
- Add to ADR section of label
- Add to Precautions/Warnings section
- Enhancement of Warnings ....Boxed
- "Dear Health Care Professional/Doctor" letter
- Modify approved indications
- Move to 2nd-line status
- Restricted distribution/prescribing/registry
- Market withdrawal/suspension

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Conclusions

- Spontaneous reporting systems are the most common methodology used to generate and detect new and rare signals
- In spite of limitations spontaneous reports of AEs have been instrumental in most safety-related drug withdrawals and labeling changes

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