Adverse Drug Reactions in the Elderly and Pharmacovigilance

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Objectives of this Presentation

- List risk factors for adverse drug reactions (ADRs) in the elderly
- Describe tools to identify potentially inappropriate medications for the elderly (Beers and STOPP criteria)
- Define pharmacovigilance and differentiate active versus passive surveillance
- Tell why it's important to report serious adverse drug reactions into passive (voluntary) surveillance systems
- Describe the EudraVigilance Adverse Event Reporting System and Netherlands Pharmacovigilance Centre Lareb
- Explain a methodology for interpreting pharmacovigilance data
Aging and Risk of ADRs

• Use of more medication - Potential side effects, interactions

• Organic changes with aging
  – Absorption (↓ intestinal motility)
  – Distribution (↓ liver, ↓ circulation, ↓ serum proteins, ↑ permeability of blood brain barrier)
  – Metabolism (↓ liver function)
  – Excretion (↓ liver and ↓ kidney)
Risk Factors for Adverse Drug Reactions in Elderly Patients\textsuperscript{2,3,4}

Table 1. The GerontoNet ADR risk score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four or more co-morbid conditions</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Liver disease\textsuperscript{a}</td>
<td>1</td>
</tr>
<tr>
<td>No of drugs</td>
<td></td>
</tr>
<tr>
<td>$&lt; 5$</td>
<td>0</td>
</tr>
<tr>
<td>5–7</td>
<td>1</td>
</tr>
<tr>
<td>$\geq 8$</td>
<td>4</td>
</tr>
<tr>
<td>Previous ADR</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure\textsuperscript{b}</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Defined as transaminases greater than twice normal limit.
\textsuperscript{b}Defined as creatinine clearance $\leq 60$ ml/min.

- Developed and validated in 2010, scores of 4 or more suggest increased risk, best predictors.\textsuperscript{3}
- Follow-up study showed that the scoring system alone may miss up to 40% of ADRs.\textsuperscript{4}
Drugs of Concern in Elderly

• Beers criteria $^5$ – list of potentially inappropriate medicines (PIMs) in older persons (age >64)
  – 53 medications or medication classes
  – 3 categories:
    1. PIMs to avoid in older adults,
    2. PIMs to avoid in older adults with certain diseases and syndromes
    3. Medications to be used with caution in older adults

• Updated in 2012 by the American Geriatric Society with assessment of strength of recommendation and quality of evidence
Drugs of Concern in Elderly\textsuperscript{6,7}

- Screening Tool Of Older Persons’ potentially inappropriate Prescriptions (STOPP) includes 65 criteria involving:
  - Drug–drug interactions
  - Drug–disease interactions
  - Drugs which adversely affect older patients at risk of falls
  - Duplicate drug class prescriptions
Comparison of STOPP and Beers Criteria

- 715 admissions of elderly to a hospital included
- Identified PIMs by STOPP and 2002 BEERS criteria
- Determined if causal relationship between admission and PIMs were present
- Results: Median age = 77, median Rxs = 6
  - STOPP results: 336 PIMs (35% of patients) with adverse drug reaction (ADR) in 33% of those with PIMS
  - Beers’ results: 226 PIMs (25% of patients), with ADR in 18.5%
  - STOPP-related PIMs associated with 11.5% of admissions
  - Beers-related PIMs associated with 6% of admissions
Literature Review of STOPP Criteria

- Identified 12 observational studies and 1 randomized trial
- Range of PIPs by STOPP was 21% to 79%
  - However, studies have different populations and designs
  - Compared to 2002 Beers criteria, STOPP usually identifies more PIPs
- Patients with STOPP-based PIPs = 85% higher risk of ADRs but no relation found between BEERS and risk of ADRs
- Limitation – Lack of evidence for improved outcomes or lower costs associated with STOPP
Adverse Drug Reaction

• An unexpected or unwanted reaction associated with a medical treatment
  – Causality not necessarily determined
Serious Adverse Drug Reactions

• Any adverse reaction that:
  – Is life threatening
  – Causes hospitalization or prolongs hospitalization
  – Results in death
  – Results in persistent of significant disability or incapacity
  – Causes a fetal or genetic abnormality
  – Requires intervention to prevent permanent impairment or damage or to prevent any of the outcomes above

European Medicines Agency (EMA)

- www.EMA.europa.eu
- Activities
  - Approval of pharmaceutical products
  - Inspection of manufacturers
  - Provide guidances to manufacturers
  - Monitor pharmaceuticals throughout life cycle
  - Protect clinical trial participants
Drug Development Process

Preclinical Phase

- IND Application
  - Initial Synthesis
  - Animal Testing

Clinical Phase

- Phase I
- Phase II
- Phase III

NDA Review Phase

- NDA Submitted
- NDA Approved

Post-Marketing Phase

- Phase IV
- Adverse Reaction Reporting
- Surveys/Sampling Testing
- Inspections

Range 1-3 Yrs.
Avg: 18 Mos.

Range 2-10 Yrs.
Avg: 5 Yrs.

Range 2 Mon – 7 Yrs.
Avg: 24 Mos.

Average of Approximately 100 Months From Initial Synthesis to Approval of NDA

From: http://www.slideshare.net/rajsadare/drug-development-life-cycle

Pharmacovigilance

• “Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.“

• Occurs both pre- and post-marketing:
  – Pre – To identify adverse reactions for the package insert.
  – Post - Once a product is marketed, data are used to assess safety in “real world” settings.
Active Pharmacovigilance

• Active – Monitor patients receiving the medicine for adverse events
  – Patient registries
    • Thalidomide – System for Thalidomide Education and Prescribing Safety (STEPS)
    • Tysabri – TOUCH http://www.tysabri.com/about/safety
  – Studies required upon marketing approval
    • Post-authorisation safety studies (PASS) mandated by EMA
    • Risk Evaluation and Mitigation Strategies (REMs) by the FDA
Example for Mycophentolate


• Healthcare providers who prescribe mycophenolate will receive training.
  Each prescriber will be provided with the Mycophenolate Program Brochure for Healthcare Providers. The brochure includes the following information:
  i. The risk of first trimester pregnancy loss and congenital malformations
  ii. Importance of educating females of reproductive potential about the increased risk
  iii. Importance of prescribers providing or facilitating patient education, including acceptable methods of contraception
  iv. Only prescribing mycophenolate to a pregnant patient if the benefits of initiating or continuing treatment outweigh the risk of fetal harm
  v. Importance of reporting to the Pregnancy Registry any pregnancies that occur during mycophenolate treatment or within 6 weeks following discontinuation of treatment
  vi. Importance of encouraging pregnant patients to participate in the Pregnancy Registry
  vii. Importance of obtaining a signed Patient-Prescriber Acknowledgement Form

• Active Pharmacovigilance: Mycophenolate sponsors will maintain a centralized pregnancy registry for females who become pregnant and consent to participate.
Passive Pharmacovigilance

• Analysis of health care data collected for another purpose
  – Large healthcare data bases
  – Governmental healthcare data
• Voluntary reporting of adverse events to EMA
## Active vs. Passive Pharmacovigilance

<table>
<thead>
<tr>
<th>Active</th>
<th>Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costly</td>
<td>Low cost</td>
</tr>
<tr>
<td>Specific criteria for adverse reaction</td>
<td>Impacted by the reporter</td>
</tr>
<tr>
<td>Details are designed into data collection</td>
<td>Impacted by the reporter</td>
</tr>
<tr>
<td>Specific patient population</td>
<td>Broad, heterogeneous population</td>
</tr>
<tr>
<td>Difficult to detect rare events</td>
<td>Rare events detected</td>
</tr>
<tr>
<td>All events are captured</td>
<td>Unknown number of missing events</td>
</tr>
<tr>
<td>Can calculate incidence rate</td>
<td>Cannot determine incidence</td>
</tr>
</tbody>
</table>
# Active vs. Passive Pharmacovigilance

<table>
<thead>
<tr>
<th>Active</th>
<th>Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costly</td>
<td>Low cost (+)</td>
</tr>
<tr>
<td>Specific criteria for adverse reaction (+)</td>
<td>Determined by the reporter</td>
</tr>
<tr>
<td>Details are designed into data collection (+)</td>
<td>Determined by the reporter</td>
</tr>
<tr>
<td>Specific patient population (+/-)</td>
<td>Broad, heterogeneous population (+/-)</td>
</tr>
<tr>
<td>Difficult to detect rare events</td>
<td>Rare events detected (+)</td>
</tr>
<tr>
<td>All events are captured (+)</td>
<td>Unknown number of missing events</td>
</tr>
<tr>
<td>Can calculate incidence rate (+)</td>
<td>Cannot determine incidence</td>
</tr>
</tbody>
</table>
Regulatory Pharmacovigilance Surveillance Systems

- **EMA = EudraVigilance**: Web-based information system since 2001.
  - Both commercial and non-commercial organisations and individuals report suspected unexpected serious adverse reactions (SUSARs).
  - EudraVigilance Clinical Trial Module (EVCTM)
  - EudraVigilance Post-Authorisation Module (EVPM)

- **FDA = MedWatch** (includes EMA reports for drugs marketed in US)

- Adverse events are reported internationally to all countries with marketing approval
Netherlands PharmacoVigilance

• Netherlands Pharmacovigilance Centre Lareb
• Maintains a database of adverse reactions submitted to Lareb
  – http://databank.lareb.nl/Bijwerkingen?lang=nl
• Exercise: Go to database and search for reactions from a drug you or your family member has received.
Passive Surveillance System

- **MedWatch**
  - 2002: 200,000 events per year
  - 2010: 680,000 events per year
  - 2014: 1 million events per year, (estimate)
  - MedDRA used for categorizing reactions
  - Estimated to represent 1 to 10% of the actual # of events
Why health professionals report to MedWatch/EudraVigilance

• "MedWatch is one of the lines of defense against products that are contaminated or that pose risks that weren't previously known," said Anna Fine, Pharm.D., director of FDA's Health Professional Liaison Program.

• A clinician or researcher inside or outside FDA or EMA might first suspect a link between a problem and a drug or other product.

• Reporting (MedWatch or EudraVigilance) becomes a useful database that experts can search for additional clues.

• Only 1 to 10% of sADRS are reported to FDA/EMA.
Medwatch Reports by Country

![Bar chart showing Medwatch reports by country from 2000 to 2010. The chart compares reports from domestic, foreign, and unknown origins. The highest number of reports is in 2010 with 451,207 reports, followed by 212,251 reports in 2009.]
Medwatch Reports by Reporter

- Consumer
- Other
- Pharmacist
- Physician
Medwatch Reports by Patient Outcomes

- Serious
- Death

2000 to 2010: Graph showing increasing trend with 471,291 serious reports in 2009 and 82,724 death reports in 2010.
Typical MedWatch Report Summary

**Synopsis (auto-generated)**

The patient is a (age unknown) male, with reports of ABDOMINAL PAIN, BLADDER SPASM, CHOROID MELANOMA, CONSTIPATION, CYSTITIS, DEHYDRATION, DEPRESSION, HEMIPARESIS, MUSCLE SPASTICITY, NEUROGENIC BLADDER and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. The suspect drug is TYSABRI, and the patient also reported taking 19 other medications.

A total of 4 reports have been submitted for this case. The selected report is the most current record.

**Sources**
- Health Professional
- Study

**Outcomes**
- Hospitalization

**Reactions**
- ABDOMINAL PAIN
- BLADDER SPASM
- CHOROID MELANOMA
- CONSTIPATION
- CYSTITIS
- DEHYDRATION
- DEPRESSION
- HEMIPARESIS
- MUSCLE SPASTICITY
- NEUROGENIC BLADDER
- PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

**Drugs**

<table>
<thead>
<tr>
<th>Mapped Drug Name</th>
<th>Drug Verbatim</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYSABRI</td>
<td>TYSABRI</td>
</tr>
<tr>
<td>WELLBUTRIN (BUPROPION)</td>
<td>WELLBUTRIN</td>
</tr>
<tr>
<td>VALIUM</td>
<td>VALIUM</td>
</tr>
<tr>
<td>SERZONE</td>
<td>SERZONE</td>
</tr>
<tr>
<td>LISINOPRIL (LISINOPRIL)</td>
<td>LISINOPRIL</td>
</tr>
<tr>
<td>GALANTAMINE</td>
<td>RAZADYNE</td>
</tr>
<tr>
<td>AMANTADINE HYDROCHLORIDE</td>
<td>AMANTADINE HCL</td>
</tr>
<tr>
<td>BACLOFEN</td>
<td>BACLOFEN</td>
</tr>
<tr>
<td>FIORINAL (ACETYLSALICYLIC ACID,BUTALBITAL,CAFFEINE,PHENACETIN)</td>
<td>FIORINAL</td>
</tr>
<tr>
<td>FLEXERIL</td>
<td>FLEXERIL</td>
</tr>
<tr>
<td>MIRALAX</td>
<td>MIRALAX</td>
</tr>
<tr>
<td>NEURONTIN</td>
<td>NEURONTIN</td>
</tr>
<tr>
<td>PERCOCET (OXYCODONE HYDROCHLORIDE,OXYCODONE TEREPTHHALATE,PARACETAMOL)</td>
<td>PERCOCET</td>
</tr>
<tr>
<td>PREVACID</td>
<td>PREVACID</td>
</tr>
<tr>
<td>GALANTAMINE HYDROBROMIDE</td>
<td>GALANTAMINE HYDROBROMIDE</td>
</tr>
<tr>
<td>VERAPAMIL (VERAPAMIL)</td>
<td>VERAPAMIL</td>
</tr>
<tr>
<td>VESICARE</td>
<td>VESICARE</td>
</tr>
<tr>
<td>ZANAFLEX</td>
<td>ZANAFLEX</td>
</tr>
<tr>
<td>VITAMINS</td>
<td>VITAMIN CAP</td>
</tr>
<tr>
<td>DETROL (TOLTERODINE L-TARTRATE)</td>
<td>DETROL</td>
</tr>
</tbody>
</table>
Causality

• When reported, based upon impression of reporter
  – Primary suspect
  – Secondary suspect
  – Concomitant

• EMA does not attempt to determine causality

• In practice Naranjo algorithm is often used

<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>Are there any previous conclusive reports on this reaction?</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Did the adverse event appear after the suspected drug was administered?</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Did the adverse reaction reappear when the drug was readministered?</td>
<td>2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Are there alternative causes (other than the drug) that could have caused the reaction?</td>
<td>-1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>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></td>
</tr>
<tr>
<td>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></td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Was the adverse event confirmed by any objective evidence?</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Strengthening Signal Detection

• Review of narrative summaries obtained through Freedom of Information Act
  – Redacted for confidentiality and trade secrets
  – Identify supporting documentation from case studies, other ADR databases
  – Mechanistic explanations from basic research
Overview of RADAR

- Research on Adverse Drug events And Reports
- Initiated in 1998

RADAR/SONAR Methodology

Figure: Flowchart of RADAR Investigations

1. Possible Occurrence of a Serious ADR
   - Review by Senior Staff
   - Preliminary Literature Review
   - Local Expert Opinion
2. Novel and Significant ADR?
   - Yes: Request and Review Sample of Additional FDA Case Reports
     - Request IRB Approvals at Collaborating Institutions
     - Extensive Literature Review
     - Hypothesis Generation
   - No: Stop Investigation
3. Summary of Early Results
   - Pathophysiology Clear?
     - Yes: Solicit Data From Other Sources
       - Manufacturer
       - Physicians
       - Clinical Centers
       - Final Analysis
       - Disseminate Results to FDA, Manufacturers, Conferences, Journals, News Media
     - No: Recruit Scientists With Specific Expertise
6. Possible Dissemination of Early Results
   - Preliminary Analysis
   - Review and Classify FDA Data
   - Customize Case Classification Form
   - Hypothesis Generation
RADAR 1998 to 2005

• First 23 events identified by RADAR
  – Median time from approval = 3 years (Range 0-17 years)
  – 9 events identified in off-label settings
Table 3. Timing of and Inconsistencies in Dissemination of Information for Serious ADRs Identified by Pharmaceutical Manufacturers and MedWatch*

<table>
<thead>
<tr>
<th>Drug or Device</th>
<th>ADR</th>
<th>FDA Approval</th>
<th>RADAR Index Case</th>
<th>Black Box</th>
<th>Warning</th>
<th>Precaution</th>
<th>Adverse Event</th>
<th>Dear Doctor Letter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thienopyridines</td>
<td>TTP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td>1997</td>
<td>1998</td>
<td>2000†</td>
<td></td>
<td></td>
<td></td>
<td>2000†</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td></td>
<td>1989</td>
<td>1996</td>
<td>1998†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoetins</td>
<td>PRCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eprex (non-US)</td>
<td>None</td>
<td></td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Procrit/epogen</td>
<td></td>
<td>1988</td>
<td>2002</td>
<td></td>
<td>2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin</td>
<td></td>
<td>2001</td>
<td>NA</td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td>Drug-eluting coronary stents</td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus-eluting cardiac stent</td>
<td></td>
<td>2003</td>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2003</td>
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<tr>
<td>Paclitaxel-eluting cardiac stent</td>
<td></td>
<td>2004</td>
<td>2004</td>
<td></td>
<td></td>
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<tr>
<td>Nonsteroidal anti-androgens</td>
<td>Pneumonitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td></td>
<td>1989</td>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicalutamide</td>
<td></td>
<td>1995</td>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2001</td>
</tr>
<tr>
<td>Other agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolendronate</td>
<td>Osteonecrosis</td>
<td></td>
<td>2001</td>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td>2004</td>
</tr>
</tbody>
</table>

*The data represents the timing and nature of dissemination of information for serious ADRs identified by pharmaceutical manufacturers and MedWatch. The table lists the drug or device, ADR, and the timing of FDA approval, RADAR index case, black box warning, precaution, adverse event, and dear doctor letter.
Thrombotic Thrombocytopenic Purpura (TTP) associated with Ticlopidine and Clopidogrel

• TTP = life-threatening, multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic changes, renal failure, and fever

• Cause of acute TTP: transient immune dysregulation and selective antigenic targeting of a metalloprotease that degrades large multimers of factor VIIIIR

• Incidence of ticlopidine-associated TTP is 1 in 1600, with mortality rate of 33%
  – Plasmapheresis: decreased mortality to 18.3%
TTP: Clopidogrel

- 50 reports of clopidogrel-associated TTP
  - 13 from RADAR active surveillance
  - 24 from pharmaceutical suppliers
  - 13 cases in MedWatch
- First year of marketing
  - 11 from RADAR
  - 6 from pharmaceutical suppliers
  - 0 cases in MedWatch

Effect of Plasmaphoresis in Clopidogrel TTP

- Plasmaphoresis in 39 cases (29 in final analysis)
  - n = 18 within 3 days, survival = 100%
  - n = 11 after 3 days, survival = 3 = 627%
- Severity of TTP: Rose and Eldor scoring with 4 categories (platelet count, hemoglobin level, serum creatinine level, neurological changes).
- Hierarchically optimal classification tree analysis used for a multivariate nonlinear model for mortality.
- Potential predictors: patient age, sex, duration of clopidogrel therapy, Rose and Eldor severity of TTP score, plasmapheresis, and plasmapheresis done within 3 days of admission.
<table>
<thead>
<tr>
<th></th>
<th>Active Surveillance (n=13)</th>
<th>Suppliers’ Reports (n=24)</th>
<th>FDA Reports (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reporting timeliness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Follow-up information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reports requested, n</td>
<td>13</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Reports received, n</td>
<td>13</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Requests for additional information which resulted in additional data, %</td>
<td>100</td>
<td>71</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>TTP diagnosis,</strong> %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>100</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Partially complete</td>
<td>0</td>
<td>79</td>
<td>69</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td><strong>Treatment,</strong> %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>100</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>Partially complete</td>
<td>0</td>
<td>47</td>
<td>83</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td><strong>Association with clopidogrel,</strong> %</td>
<td>100</td>
<td>58</td>
<td>23</td>
</tr>
<tr>
<td>Complete</td>
<td>0</td>
<td>33</td>
<td>54</td>
</tr>
<tr>
<td>Partially complete</td>
<td>0</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0</td>
<td>17</td>
<td>54</td>
</tr>
<tr>
<td><strong>Diagnostic certainty,</strong> %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable cases</td>
<td>92</td>
<td>45</td>
<td>23</td>
</tr>
<tr>
<td>Possible cases</td>
<td>8</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td>Incompletely reported</td>
<td>0</td>
<td>17</td>
<td>54</td>
</tr>
</tbody>
</table>

*Timeliness of TTP reporting: Total possible/probable cases identified in the first year of drug marketing (November 1998–December 1999)
Classification tree analysis model for predicting mortality.

Zakarija A et al. Stroke. 2004;35:533-537
Epoetin PRCA

- Pure red cell aplasia: Antibody-mediated syndrome of anemia associated with a low reticulocyte count, an absence of erythroblasts in the bone marrow, resistance to recombinant human erythropoietin (epoetin) therapy, and neutralizing antibodies against erythropoietin.

- Data: 506 MedWatch reports, screened to 191 cases
  - Excluded: absence of documentation of epoetin-associated antibodies (208 cases), the use of multiple epoetin products (44 cases), duplicate reports (34 cases), and features inconsistent with the diagnosis of pure red-cell aplasia (29 cases)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epoetin Alfa</th>
<th>Epoetin Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eprex (N=175)</td>
<td>Epogen (N=5)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>Range</td>
<td>17–86</td>
<td>11–77</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>Anemia from chronic kidney disease (%)</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Subcutaneous administration (%)</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Country (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>France</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Australia</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Italy</td>
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<td>0</td>
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<tr>
<td>United States</td>
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<td>100</td>
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<tr>
<td>Other European countries</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Asia, Africa, and South America</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
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</tr>
</tbody>
</table>

In Germany and Italy there were the same number of case reports within each year.

HSA denotes human serum albumin. Epogen is also marketed as Procrit, and Neorecormon as Recormon.
Epoetin PRCA

• Conclusions – Manufacturing and administration concerns
  – Eprex, marketed outside the US = 92% of cases
  – Indication and administration route: >75% PRCA patients, chronic kidney disease, received subcutaneous doses of epoetin
  – Vehicles: Eprex (polysorbate 80 and glycine) Neorecormon (polysorbate 20, glycine, calcium chloride, urea, and a 5-amino-acid complex in Neorecormon)
  – Mfr. procedures for handling the product
  – Organic compounds leached by polysorbate 80 from the rubber plungers used in the prefilled syringes of Eprex
• Changes in manufacturing addressed problem
Taxoids

• Anaphylactic reactions more common for paclitaxel formulated with Cremaphor EL™ and docetaxel formulated with Tween 80™ than for albumin-bound paclitaxel (Abraxane®)

• Prophylaxis:
  – Paclitaxel prophylactic pre-medications (PPM): corticosteroids, diphenhydramine (a histamine-1 (H-1) receptor antagonist), and histamine-2 (H-2)
  – Docetaxel PPM: corticosteroids for 3 days
  – Albumin-bound paclitaxel: no prophylaxis

• FDA data summary
Taxoids and Anaphlyactic Reactions

- Anaphylaxis reported to FDA
  - Paclitaxel: n = 693; Docetaxel: n = 290; Albumin-bound paclitaxel = 0.
  - EBGM: significant for paclitaxel (2.50, 95% CI 2.32-2.70).
  - EBGM: not significant for docetaxel (1.74, 95% CI 1.57 – 1.96)
- Appropriate prophylaxis (about 33% use) lowered mortality in paclitaxel (p<0.01) (17.7% vs. 31.7%), but not in docetaxel (52.3% vs. 55.2%).
- Suggest re-evaluation of prophylaxis for docetaxel and reinforce proper use of prophylaxis for both drugs
SONAR

• University of South Carolina, College of Pharmacy
• SONAR = Southern Oncology Network on Adverse Reactions
• Team led by Charles L Bennett, MD, PhD
Conclusions

• There are identifiable risk factors for adverse drug reactions (ADRs) in the elderly and tools to help identify potentially inappropriate medications for the elderly
• Pharmacovigilance is the study of adverse drug reactions and may be carried out using active and/or passive surveillance
• It’s important to report serious adverse drug reactions into passive (voluntary) surveillance systems
• EudraVigilance Adverse Event Reporting System and Netherlands Pharmacovigilance Centre Lareb are available data sets to study adverse reactions
• Methods are key in interpreting pharmacovigilance data
• FDA AERS data can be used to support research projects regarding serious ADRs
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References


