The Role of Epidemiology in the Pharmaceutical Industry – Safety and Effectiveness

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JOHNS HOPKINS UNIVERSITY SCHOOL OF PUBLIC HEALTH
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Conflict of Interest Declaration

- Independent consultant
- Previously employed:
  - Merck & Co, Inc.,
  - National Heart, Lung and Blood Institute, NIH
The Role of Epidemiology in the Pharmaceutical Industry – Safety and Effectiveness

Agenda:
- Disease epidemiology, natural history, biomarkers
- Clinical and patient measurement
- Safety and Effectiveness—understanding safety during development and post-marketing and effectiveness post-marketing
Merck Epidemiology Department Founded in 1985 by Dr. Harry Guess

Photograph is from the early 1990s

By 2014 there were approximately 65 members in the Department in 4 countries
Epidemiology is Foundation for Drug and Vaccine Development

“...to understand the Drug or Vaccine, it is necessary to understand the Disease*”

Harry Guess – Merck Vice President and Head Epidemiology (1985-2003)

Early Epidemiology Data Builds Foundation for Drug/Vaccine Development

- Understand the disease and the populations impacted
  - E.g. Prevalence, incidence, burden and natural history, risk factors, important co-morbidities and concomitant medications, biomarkers, genotypes, serotypes...

- Understand outcomes important to and impacting patients
  - E.g. Patient Reported Outcomes (PRO), Clinical Outcome Assessments (COA)

- Linking surrogate measures with disease outcomes, validating outcomes, biomarkers and genetic markers
## Activities in the Phases of Drug and Vaccine Development

<table>
<thead>
<tr>
<th>Preclinical Development</th>
<th>I</th>
<th>IIa&amp;b</th>
<th>III</th>
<th>IV/V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discovery</strong> - chemical &amp; biological characterization</td>
<td>Ph I studies healthy volunteers to understand ADME, PK, PD, drug interactions, special groups</td>
<td>Proof of Concept and Dose Ranging randomized clinical trials - dose(s), efficacy and safety</td>
<td>Ph III pivotal randomized clinical trials - characterize efficacy and safety</td>
<td>Post-marketing clinical trials - additional patient subgroups, new indications, combination therapies, endpoint trials</td>
</tr>
<tr>
<td><strong>Safety &amp; toxicity studies</strong> in animals; formulation development</td>
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</tbody>
</table>
# Epidemiology Activities In Phases of Drug and Vaccine Development

<table>
<thead>
<tr>
<th>Preclinical Development</th>
<th>I</th>
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</thead>
</table>

### Descriptive Epidemiology

- Studies to understand disease and population

### Trial Planning

- Activities/recruitment issues: selecting RCT design, population, treatment, duration

### Development

- **I: Preclinical Development**
  - Develop functional and/or patient reported outcomes (PROs) or clinical endpoints (COAs)

- **IIa&b: Clinical Development I**
  - Validate PROs/clinical endpoints

- **III: Clinical Development II**
  - Risk management planning; Pharmacoepidemiology studies/analyses to address product safety & understand risks in population with disease

- **IV/V: Clinical Development III**
  - Linking biomarkers/genetic markers to disease outcomes
Early Development Use of Epidemiology Studies/Activities

- **Clinical** – help define study endpoints, population, duration of trial, serotypes, interpret clinical trial results based on natural history of disease and expected AEs, develop/validate/standardize clinical measures

- **Regulatory** – understand background rates of Adverse Events in population, define importance of disease in specific subgroups, compliance with PRO Guidance, help define what is clinically meaningful change or effect size to patients

- **Commercial** – help define market potential through prevalence and incidence estimates, define burden of illness, provide data for health economic models for reimbursement dossiers
Planning Type 2 Diabetes Clinical Trials

Purpose: Describe prevalence and incidence data & progression rates for Type II Diabetes Mellitus for clinical trial planning
Data Source: Diabetes Atlas, International Diabetes Federation
Determine Ideal Duration of Treatment for T2DM Trial

Time to A1c>8% with MF+SU

Baseline A1c
- >10%
- 9-9.9%
- 8-8.9%
- 4-7.9%

Proportion with A1c>8.0%

Trial duration of 2 years duration likely sufficient to show differences in durability

Time from sulfonylurea initiation (years)

Understand Herpes Zoster Burden of Illness

Problem: What is the medical need to vaccinate population against Herpes Zoster and at what ages is vaccine most needed?

Study Design: Analyses of patient level electronic medical record databases in two United States patient care databases capturing physician visits, medication use and hospitalizations due to Herpes Zoster. Charts reviewed for cases.

Herpes Zoster (HZ) Incidence by Age and Sex

- Average of 3 ambulatory visits per Herpes Zoster patient
- >70% of HZ cases receive antiviral drugs and 4% of HZ cases hospitalized
Burden Herpes Zoster in Immunocompromised Patients

- Problem: What is the incidence of Herpes Zoster in Solid Tumor (STM) and Hematological Malignancy (HM) populations and how does that compare to general population?

- Study Design: Retrospective cohort study (N=13,759) with complete chemotherapy data in Kaiser Permanente Northern California, US enrolled from 2001-2005
  - Chart review for all cases and adjudication to validate zoster cases
Compared to individuals of similar age and sex in the general population, rates of HZ were approximately 5-fold higher in patients with HM and 1.8-fold higher in patients with STM.
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- Clinical and patient measurement
- Safety and Effectiveness – understanding safety during development and post-marketing and effectiveness post-marketing
PRO/COA Development and Validation
Does the drug work or is the measure poor?

- Measures should show:
  - Content Validity - valid and relevant to patients
  - Construct Validity - valid for the domain it measures
  - Test-Retest Reliability - measured consistently
  - Responsiveness - sensitive to change in health state
  - Linguistically Valid - endpoint understandable in other cultures

Accurate, but not precise

Precise, but not accurate
PRO and COA Development and Validation
Does the drug work or is the measure poor?

- Measures should show:
  - Content Validity - valid and relevant to patients
  - Construct Validity - valid for the domain it measures
  - Test-Retest Reliability - measured consistently
  - Responsiveness - sensitive to change in health state
  - Linguistically Valid - endpoint understandable in other cultures


- Clinical Outcome Assessment Qualification Program
<table>
<thead>
<tr>
<th>Program</th>
<th>Measure</th>
<th>Intent – To Assess:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Symptom diary</td>
<td>daily asthma symptom frequency and severity</td>
</tr>
<tr>
<td>Overactive Bladder</td>
<td>Voiding diary</td>
<td>frequency of voids, incontinence episodes and urgency in a 7-day diary</td>
</tr>
<tr>
<td>Flushing</td>
<td>FSQ, FIQ</td>
<td>Severity, bother and duration of niacin-induced flushing in a 7-day daily diary; impact of niacin-induced flushing</td>
</tr>
<tr>
<td>Flu</td>
<td>IIWS and ISS</td>
<td>daily impact and severity of flu symptoms</td>
</tr>
<tr>
<td>Chemo-induced Emesis</td>
<td>FLIE</td>
<td>impact of chemotherapy-induced nausea and vomiting on daily life (validated with longer recall by Epi)</td>
</tr>
<tr>
<td>Acne</td>
<td>AcneQoL</td>
<td>impact of facial acne on self-perception, role-emotion, role-social, symptoms</td>
</tr>
<tr>
<td>COPD</td>
<td>CSD</td>
<td>COPD symptoms in a 7-day diary</td>
</tr>
<tr>
<td>Hot flash</td>
<td>Hot flash eDiary</td>
<td>hot flash occurrence and severity</td>
</tr>
<tr>
<td>Cough</td>
<td>Cough severity diary</td>
<td>daily attributes of cough severity</td>
</tr>
<tr>
<td>Pediatric asthma</td>
<td>Pediatric Asthma Caregiver Diary</td>
<td>daily symptom frequency and severity in children 2-5 yr with moderate asthma, in children 6 months–2 yr with persistent symptoms following RSV Bronchiolitis</td>
</tr>
</tbody>
</table>
Evaluate cognition test battery as a valid biomarker in early studies of Alzheimer’s Disease and cognitive disorders.

The Role of Epidemiology in the Pharmaceutical Industry – Safety and Effectiveness

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Development of Pharmacoepidemiology

▶ Safety is the driving force for development of pharmacoepidemiology as a unique discipline

▶ “Pharmacoepidemiology is the study of the use of and the effects of drugs and vaccines in large numbers of people.”*

▶ The realization that rare adverse effects of drugs or vaccines could be better understood through the application of epidemiological research methods gave rise to pharmacoepidemiology

Pre-Authorization Risk Management Planning

- Evaluation and management of identified adverse events from the randomized clinical trials
  - Risk Management Plans (RMPs) and Risk Evaluation and Mitigation Strategies (REMS)
- Evaluate the disease population (literature and studies)
  - Types of likely co-morbidities and concomitant medications
  - Risk factors for adverse events
  - Background rates of potential and identified adverse events that might be expected
  - Begin planning Post-Authorization Safety Study (PASS)
- Respond to Regulatory Agency questions and prepare for meetings with regulatory agencies with epidemiology data on the disease, background rates of adverse events in the disease population, and potential PASS discussion
**Background Rates of Adverse Events to Help Interpret Clinical Trial Results**


**OBJECTIVE:**
To examine the risk of acute thromboembolic cardiovascular events (TCEs) (myocardial infarction, sudden death, and stroke) with current naproxen use among patients with rheumatoid arthritis.

**METHODS:**
We studied patients aged 40 to 79 years with rheumatoid arthritis in the British General Practice Research Database, excluding those with a prior TCE and potentially confounding conditions. We matched up to 4 controls by sex, age, and site of medical practice to cases with first incident TCEs. The case diagnosis date was designated as the index date for each case and his or her controls. We categorized naproxen according to the most recent prescription prior to the index date as being current (≤30 days), past (>30 days but <365 days), or none (>365 days before index date). Using conditional logistic regression, we conducted a matched case-control analysis with adjustment for potential confounders.

**RESULTS:**
We identified 809 cases. **Current naproxen use was more common among controls (5.7%) than cases (3.2%).** Adjusting for calendar year of treatment start, systemic corticosteroid use, diabetes, and comorbidity, we found that the odds ratio (95% confidence interval) for current naproxen use was 0.61 (0.39-0.94) while that for past use was 0.87 (0.65-1.16). Secondary and sensitivity analyses supported these results.

**CONCLUSIONS:**
In this case-control study, patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major TCEs relative to those with no naproxen prescription in the past year. These results are consistent with the ability of naproxen to inhibit platelet aggregation.
Post-Authorization Safety

- **Rapidly changing** environment over past 10 years
  - Increased use of patient health care databases (claims and electronic medical records) in addition to traditional methods focused on spontaneous adverse events evaluation

- **Regulations** from US FDA and EMA requiring conduct of Post-Authorization Safety Studies (PASS)
  - FDA and EMA Initiatives to evaluate safety using observational (non-interventional studies):
    - FDA Sentinel Initiative
    - EMA Pharmacovigilance Risk Assessment Committee (PRAC) and ENCePP Initiatives
US Food and Drug Administration (FDA)

- US regulation* allows the FDA to require post-marketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of new safety information.
  - New safety information includes data about a serious risk, or an unexpected serious risk associated with use of the drug.
  - Even if serious risk is known at time of approval, additional information may be required.

In 2007, U.S. Congress passed the FDA Amendments Act mandating establishment of an active surveillance system for monitoring drugs, using patient level electronic healthcare data.

- Sentinel Initiative is FDA’s response to that mandate.
  - Goal: build and implement an active surveillance system to monitor FDA-regulated products using observational (non-interventional) study methods (goal 100 million subjects by July 2012 - met).

- Mini-Sentinel uses a distributed database of secondary patient healthcare data collected from 18 healthcare organizations in the U.S.:
  - > 35 assessments – health outcomes in individuals exposed to medical products either completed or in progress (http://mini-sentinel.org/assessments/medical_events/default.aspx)

- White Paper 11/24/2015 - Exploration of potential for Sentinel and PCORnet Data Linkages (Claims and EHR)

http://mini-sentinel.org/
European Medicines Agency (EMA)

- Post-Authorization Safety Study (PASS) is carried out after a medicine has been authorized to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures.

- Evaluate the safety and benefit-risk profile of a medicine and support regulatory decision-making:
  - identify, characterize or quantify a safety hazard;
  - confirm the safety profile of a medicine, or;
  - measure the effectiveness of risk-management measures.

- EMA Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing the protocols of imposed PASSs and for assessing their results.

Marketing-authorization holders (MAHs) are obliged to carry out **imposed PASS**
- Include studies that are a specific obligation for a marketing authorization granted under exceptional circumstances
- Other studies that the PRAC requests the MAH to carry out

**Voluntary PASS** are sponsored or conducted by MAHs on their own initiative
- PASS can be interventional or non-interventional
- EMA PASS website provides both PASS protocol and report templates
Pharmacoepidemiology in Safety Assessment and Evaluation Post-Approval

- Further understand product safety in larger populations - conduct post-approval safety and drug utilization analyses and studies
  - Patterns of drug utilization - who is using product and how product is used in real world use
  - Understand safety in subgroups and special populations
  - Understand risk factors for adverse events
  - Safety relative to other drugs for the same indication
  - Determine new or very rare adverse events
  - Understand risk as compared to benefit
  - Develop reliable methods and study designs to increase reliability of observational studies
Non-Interventional Studies

- Reflect real-world use of drug/vaccine
  - Patient groups previously not studied or inadequately studied in clinical trials

- Non-random assignment of treatment
  - May lead to spurious associations due to bias and confounding

- Careful study design can maximize probability that results are valid and reliable
  - The strength of the evidence must be grounded in results from studies that compare “like with like” and make every attempt to minimize bias
Primary data collection and analyses:
- Enroll patients and measure characteristics and outcomes prospectively
- Review and collect data from patient medical charts
- Can be tailored to the research question
- More expensive and labor intensive

Secondary data analyses (increasing use):
- Existing patient level data
  - Existing patient cohorts, registers, registries, health insurance claims, electronic medical record databases and distributed linked databases (e.g. FDA Sentinel)
- Depends on available data (size, outpatient, inpatient, duration, labs, procedures, behavioral data)
- Less expensive and less labor intensive
Examples of Regulatory Questions

- Impact of in-hospital insulin use on hypoglycemia, length of stay, in-hospital mortality and in-hospital ischemia events in insulin users versus non-users
- Incidence and prevalence of hemorrhagic and necrotic pancreatitis in T2DM and non-T2DM patients
- Prevalence of renal insufficiency among patients with osteoporosis
- Incidence and prevalence of scleroderma in women with osteoporosis
- Incidence of cancer by cancer type in patients with HIV versus general population
Baseline Characteristics of Elderly Patients (≥65 years) by Treatment Initiation

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Sitagliptin Adjusted OR (95% CI)</th>
<th>Other OAHA Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1.14 (1.08, 1.21)</td>
<td>1.14 (1.08, 1.21)</td>
</tr>
<tr>
<td>66-69</td>
<td>1.02 (0.97, 1.07)</td>
<td>0.98 (0.91, 1.05)</td>
</tr>
<tr>
<td>70-79</td>
<td>0.68 (0.64, 0.73)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.68 (0.64, 0.73)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>Race, Black</td>
<td>0.98 (0.91, 1.05)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>Newly Diagnosed T2DM</td>
<td>0.98 (0.91, 1.05)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>1 OHA</td>
<td>1.02 (0.97, 1.07)</td>
<td>0.98 (0.91, 1.05)</td>
</tr>
<tr>
<td>2 OHA</td>
<td>0.68 (0.64, 0.73)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
<tr>
<td>≥ 3 OHA</td>
<td>0.68 (0.64, 0.73)</td>
<td>0.94 (0.87, 1.02)</td>
</tr>
</tbody>
</table>

Age Ranges:
- Women
- 66-69
- 70-79
- ≥ 80
- Race, Black
- Newly Diagnosed T2DM
- 1, 2, ≥ 3 OHA
Problem: Difference in Reports for Two Hep B Vaccines in the US FDA Vaccine Adverse Event Reporting System (VAERS)

Niu et al. Comparative Safety of Two Recombinant Hepatitis B Vaccines in Children: Data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD) J Clin Epidemiol 51;6: 503–510, 1998

<table>
<thead>
<tr>
<th>Event severity</th>
<th>Days to event</th>
<th>Vaccine brand</th>
<th>Relative reporting ratio (RRR)</th>
<th>95% confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vaccine A</td>
<td>Vaccine B</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0–3</td>
<td>0.35</td>
<td>0.10</td>
<td>3.56</td>
</tr>
<tr>
<td></td>
<td>0–7</td>
<td>0.43</td>
<td>0.14</td>
<td>3.13</td>
</tr>
<tr>
<td></td>
<td>0–30</td>
<td>0.86</td>
<td>0.15</td>
<td>5.54</td>
</tr>
<tr>
<td>Serious</td>
<td>0–3</td>
<td>2.55</td>
<td>0.38</td>
<td>6.78</td>
</tr>
<tr>
<td></td>
<td>0–7</td>
<td>2.88</td>
<td>0.42</td>
<td>6.92</td>
</tr>
<tr>
<td></td>
<td>0–30</td>
<td>3.22</td>
<td>0.45</td>
<td>7.19</td>
</tr>
<tr>
<td>Nonserious</td>
<td>0–3</td>
<td>16.32</td>
<td>1.99</td>
<td>8.18</td>
</tr>
<tr>
<td></td>
<td>0–7</td>
<td>17.15</td>
<td>2.10</td>
<td>8.18</td>
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<tr>
<td></td>
<td>0–30</td>
<td>17.79</td>
<td>2.19</td>
<td>8.13</td>
</tr>
</tbody>
</table>
Vaccine Safety Datalink (VSD) Study

VSD - population based electronic data - no difference in events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age-adjusted, vaccine combination, facility-adjusted</th>
<th>Age-adjusted</th>
<th>95% CI</th>
<th>Age-adjusted</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hospitalizations</td>
<td>RR^b 1.03, 95% CI 0.93–1.13</td>
<td>RR^b 1.04</td>
<td>95% CI 0.93–1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious hospitalizations</td>
<td>RR^b 1.17, 95% CI 0.91–1.50</td>
<td>RR^b 1.25</td>
<td>95% CI 0.95–1.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ER visits</td>
<td>RR^b 0.94, 95% CI 0.89–1.00</td>
<td>RR^b 0.96</td>
<td>95% CI 0.90–1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious ER visits</td>
<td>RR^b 0.94, 95% CI 0.82–1.07</td>
<td>RR^b 0.99</td>
<td>95% CI 0.86–1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitalizations + ER visits</td>
<td>RR^b 0.96, 95% CI 0.91–1.01</td>
<td>RR^b 0.98</td>
<td>95% CI 0.92–1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious hospitalizations + ER visits</td>
<td>RR^b 1.00, 95% CI 0.89–1.13</td>
<td>RR^b 1.07</td>
<td>95% CI 0.94–1.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^aICD-9 codes selected as “serious events” possibly related to HepB vaccination.
^bRelative risk (RR).
^cConfidence intervals (CI).
Gastric and Duodenal Safety of Alendronate Cohort Safety Study

Isolated case reports of gastric ulcers after alendronate use

Cohort Study in 8 healthcare organizations in US 1995 through 1997 comparing alendronate users and unexposed patients:
  • Alendronate users (n=6,432)
  • Women with osteoporotic fracture (n=9,776)
  • Age-gender matched unexposed (n=33,176)

Results: No statistically significant differences between groups
  • Alendronate vs. unexposed (adjusted RR = 1.8, 95% CI, 0.8 – 3.9)
  • Alendronate vs. women with fracture (adjusted RR = 1.1, 95% CI, 0.6 - 2.2)

Conclusions: OPand related factors appear to play an important role in the relationship between alendronate use and confirmed GI perforation, ulcer, or bleeding

“New Users” design

- Avoid comparing new and prevalent users
  - Depletion of susceptible populations in the prevalent group may make comparison biased

- Understand who is being treated with your drug/vaccine as compared to comparator(s)
  - Describe baseline characteristics for all groups prior to conducting any comparison to determine if channeling bias is occurring where higher risk patients preferentially receive one treatment over another treatment
    - Differences may be too great to adjust statistically (e.g. propensity score) with little to no overlap in treatment patterns
Example for VTE Risk and Contraception: Consequences of Comparing All Users (Long Term and New)

The ‘all-users’ analysis reduces the VTE incidence rate for the older product by including long term users (‘prevalent’ users who started pre-2001) whose VTE risk is lower at the start of the study period.
### Impact on Venous Thromboembolism (VTE) Incidence of “all user” vs. “new user” analyses

<table>
<thead>
<tr>
<th>Study period: 2001-2007</th>
<th>All Users</th>
<th>New Users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-adjusted Incidence rate*</td>
<td>Age-adjusted Incidence rate*</td>
</tr>
<tr>
<td>NuvaRing (NR)</td>
<td>11.91</td>
<td>11.35</td>
</tr>
<tr>
<td>Levonorgestrel (LNG)</td>
<td>6.64</td>
<td>9.21</td>
</tr>
</tbody>
</table>

Need to assure that cases are truly cases

- Blinded, independent case adjudication of primary and key secondary endpoints
  - Assures that cases identified are true positive cases for analyses
  - Decreases diagnostic bias
  - Cannot decrease detection bias which can occur if healthcare provider is looking harder for the event in one group versus another group
Example of Chart Review and Adjudication in Database Study

- MMRV compared to MMR+V vaccination and Febrile Seizures evaluation

- Coding practice changes at healthcare system (Kaiser Permanente Southern California- KPSC) from 2004-2007 resulted in documented increase in seizure code use over study period
  - Adjudication likely removed most of this bias, improving validity of results

- Adjudication Committee (3 KPSC Physicians)
  - Reviewed medical records data using Brighton Collaboration definition for Febrile Seizure
  - The adjudication process identified “confirmed Febrile Seizures”
Kaplan-Meier Curves - MMRV and MMR+V
Unconfirmed Febrile Seizures
Kaplan-Meier Curves - MMRV and MMR+V
Confirmed Febrile Seizures

Days after Vaccination

Cumulative Incidence

MMRV

MMRV + V

p = 0.6617
What Do We Do When Observational Database Analyses Lead to Two Different Conclusions

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist, Gabriela Czanner, statistician, Gillian Reeves, statistical epidemiologist, Joanna Watson, epidemiologist, Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit, Valerie Beral, professor of cancer epidemiology

BMJ 2010; 341:c4444

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Chris R. Cardwell, PhD
Christian C. Abnet, PhD
Marie M. Cantwell, PhD
Liam J. Murray, MD

JAMA 2010; 304(6): 657-663
Relative Risk for Esophageal Cancer in Relation to Prescriptions of Oral Bisphosphonates in UK Primary Care Cohort

<table>
<thead>
<tr>
<th>Oral bisphosphonates</th>
<th>Prescriptions*</th>
<th>Cases/controls</th>
<th>RR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not prescribed</td>
<td>NA</td>
<td>2864/14 376</td>
<td>1.00</td>
</tr>
<tr>
<td>Prescribed</td>
<td>13.6/2.4</td>
<td>90/345</td>
<td>1.30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No of prescriptions:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-9</td>
<td>3.6/1.0</td>
<td>40/214</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>(0.66 to 1.31)</td>
<td>(0.66 to 1.31)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>21.6/3.5</td>
<td>50/131</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td>(1.37 to 2.70)</td>
<td>(1.37 to 2.70)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated duration of use‡:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 year</td>
<td>4.9/0.3</td>
<td>31/155</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>(0.66 to 1.46)</td>
<td>(0.66 to 1.46)</td>
<td></td>
</tr>
<tr>
<td>1-3 years</td>
<td>13.0/2.0</td>
<td>26/114</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>(0.73 to 1.73)</td>
<td>(0.73 to 1.73)</td>
<td></td>
</tr>
<tr>
<td>≥3 years</td>
<td>22.2/4.6</td>
<td>33/76</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>(1.47 to 3.43)</td>
<td>(1.47 to 3.43)</td>
<td></td>
</tr>
</tbody>
</table>

The risk of oesophageal cancer is increased with ≥10 prescriptions for oral bisphosphonates and with prescriptions ≥3 years.

Conclusion:
Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was *not significantly associated* with esophageal or gastric cancer.

What is Truth in Observational Safety Studies?

- Two observational comparative safety studies – one cohort and one case-control in same database – find different associations of risk of Oral BisPhosphonates and Esophageal/GI Cancers - RR < 2.0

- How should regulatory agencies respond?
  - Ask for pooled analyses of safety data from clinical trials?
  - Ask for additional observational safety studies
  - Issue a drug safety announcement (FDA Drug Safety Communication: Ongoing safety review of oral osteoporosis drugs (bisphosphonates) and potential increased risk of esophageal cancer - [07-21-2011])
    - “FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer and there are conflicting data on this risk”

- How should healthcare providers and patients respond and weigh benefit and risk?
  - Continue treatment but inform patients of potential risk? Limit treatment duration? Discontinue treatment? Make no changes until more definitive studies are done?

- What should the Pharma Company do?
**Observational CER Studies**

- Patients ‘observed’ as in normal clinical practice (‘real world setting’)  
  - Patients receive treatment per usual clinical practice prescriptions  
  - Informed consent depends on study and invasiveness of procedures  
  - Prospective or retrospective / cohort or case-control designs  
  - Usually NOT randomized

There is no perfect design – all have strengths and weaknesses

- Observational studies prone to biases (i.e., confounding, selection or information bias, surveillance bias, etc)* and limitations  
  - Study Design requires significant planning and expertise  
    - Need to account for bias and confounding  
    - For some studies can not adequately adjust for confounding  
  - Many researchers without the expertise are starting to conduct CER studies due to availability of large EMR/claims databases

*Defined on next slide
Limitations of Observational Comparative Effectiveness Methods

- Unique methodological challenges in conducting Observational Studies of Effectiveness
- Studies may be susceptible to systematic error:
  - Selection bias
  - Information bias: Exposure and/or Outcome misclassification
  - Surveillance bias: Monitoring of exposed patients may be different between groups – can result in detection or diagnostic bias
  - Channeling bias:
    - Confounding by indication: people who receive a drug are different from people who do not, in that they have an indication for therapy

Brian Strom, Medical Care. 45(10): Supplement October 2007
Effectiveness of Vaccination against Rotavirus Acute Gastroenteritis (AGE)

- Analyzed large, national US health insurance claims database
  - Linked vaccination status with healthcare outcomes for AGE

- Design: AGE outcomes among infants vaccinated with 3 doses of RotaTeq® as compared to a concurrent cohort of infants who were not vaccinated with RotaTeq® in the same time period AND received 3 doses of a reference vaccine (DTaP)

Vaccine Effectiveness Against Rotavirus Gastroenteritis in Routine Practice US National Claims Database

Infants Who Received 3 Doses of RotaTeq® vs DTaP recipients

<table>
<thead>
<tr>
<th>Medical Setting</th>
<th>Incidence Rate per 1000 person years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RotaTeq (N = 33,140) (7700 person years)</td>
</tr>
<tr>
<td></td>
<td>Concurrent Cohort (N = 27,954) (5831 person years)</td>
</tr>
<tr>
<td>Hospital</td>
<td>0</td>
</tr>
<tr>
<td>Emergency Dept</td>
<td>0</td>
</tr>
<tr>
<td>Combined (Hosp+ED)</td>
<td>0</td>
</tr>
<tr>
<td>Physician Office Visit</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Vaccine Effectiveness (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>100% (86 - 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>100% (&lt;0 -100)</td>
</tr>
<tr>
<td>Emergency Dept</td>
<td>100% (87 - 100)</td>
</tr>
<tr>
<td>Combined (Hosp+ED)</td>
<td>96% (76 - 100)</td>
</tr>
</tbody>
</table>
Angiotensin II-Receptor Blockers in Randomized Clinical Trials

- Candesartan significantly reduced all-cause mortality, CV death, and HF hospitalizations 18% (HR 0.82; 95% CI 0.74 to 0.90; P<0.001) in patients with CHF and LVEF < or =40% when added to standard therapies including ACE-inhibitors, BBs and aldosterone antagonists.

- Candesartan greater BP lowering than Losartan in RCT (peak BP 15.2-11.6 mmHg vs. 12.6-10.1 mmHg; p<0.05 and trough SBP/DBP 13.3/10.9 mmHg vs. 9.8/8.7 mmHg p < 0.001 with candesartan vs losartan, respectively).

- No head to head RCTs comparing Candesartan to Losartan on outcomes of CV death or mortality.

1-yr survival 90% (95% CI, 89%-91%) for candesartan vs. 83% (81%-84%) for losartan & 5-yr survival was 61% (54%-68%) vs. 44% (41%-48%), respectively (log-rank $P < .001$); multivariate PS adjustment, HR for mortality for losartan compared with candesartan was $1.43$ (95% CI, 1.23-1.65; $P < .001$)

Eklind-Cervenka M at al. JAMA 2011;305:175-82
Losartan was not associated with increased all-cause mortality (adjusted hazard ratio [HR], 1.10; 95% CI, 0.96-1.25) or CV mortality (adjusted HR, 1.14; 95% CI, 0.96-1.36) compared to Candesartan.
Two Comparative Effectiveness Studies in Nordic Registries: Different Results – WHY?

- Confounding and bias
  - Different baseline characteristics
    - Co-morbidities
    - Concomitant medications
    - Duration of HF and duration of treatment
    - Age
  - Not a new users analyses; mixed prevalent and incident users
  - Missing data on important variables
- Modeled dose comparisons:
  - Large differences in % users achieving target dose; users of Candesartan more likely to achieve high-dose treatment as compared to Losartan users
    - higher average relative dose among Candesartan users may have led to overestimation of overall comparative effectiveness
Review the Methods and Check Results

- Evaluate results clinically, methods and operationally:
  - Check the Data
  - Check the Analytic Programs
  - Conduct Descriptive Statistics (by age, gender, seasonal trends, study site)
  - Evaluate Time from Exposure to Adverse Event
  - Adjust for Additional Confounders
  - Use Other Comparison Groups
  - Chart Review to Validate Cases
  - Compare with Other Existing Data
  - Conduct Studies with New Data
  - Compare Similar Outcomes
  - Include Sensitivity Analyses

Modified from Kulldorff, Yih, presentations for US CDC Vaccine Safety Datalink
The Role of Epidemiology in the Pharmaceutical Industry – Safety and Effectiveness

- Growing role of Epidemiology in Pharmaceutical Industry
  - Understanding the disease
  - Validating measures
  - Safety and Effectiveness – Benefit-Risk

- Challenges:
  - Data
  - Methods
  - Conflicting studies
  - Perception of Industry vs Academia – different conflicts of interest
  - Outcomes Research vs Epidemiology
Questions?

“...to understand the Drug, it is necessary to understand the Disease”
Harry Guess

"It is more important to know what sort of person has a disease than to know what sort of disease a person has"
Hippocrates