Pharmacoepidemiology

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What is pharmacoepidemiology?

- study of drug efficacy, toxicity and patterns of use in **large populations**
- unlike pharmacoconomics, does not look at cost related outcomes
- uses epidemiologic methods to answer drug related questions in large populations
Pharmacoepidemiology - collection of several disciplines

- Biostatistics
- Epidemiology
- Medicine
- Computer programming
- Pharmacology
- Administrative data
example with **Nifedipine (Adelat XL)**

- **basic pharmacology**
  - Ca^2+ blockers block calcium influx

- **clinical pharmacology**
  - nifedipine’s starting dose in a 50 year old is 30mg daily

- **pharmacoepidemiology**
  - the relative risk of MI in nifedipine users compared to thiazide users among cohort of antihypertensive users is 2.1
Where is pharmacoepidemiology most effective?

- effective tool in identifying rare ADEs
- pharmacovigilance
  - requires large sample size to detect
- some examples of rare ADEs
  - bisphosphonates/jaw necrosis
  - NSAIDs/tendon rupture
  - dopamine agonist/heart valve abnormalities
History of pharmacoepidemiology: the thalidomide tragedy

- introduced in the 1960s
- marketed as thalidimide (Contergan®)
- used to control nausea in pregnancy
- reports of limb abnormalities
- need for pharmacovigilance
Study designs in pharmacoepidemiology

- Case-control studies
- Cross-sectional study
- Case-cross over study
- Cohort studies
Limitations of RCTs

- Underpowered to detect rare adverse events
- Usually short follow up
- Difficult to apply results to a real clinical setting
- Difficult to execute; logistics, costs
Case-control studies

- Ideal for rare adverse events
- First step: Identify all cases
- Second step: Select controls (none cases)
- Compare exposure distribution between cases and controls
- Calculate an odds ratio
Calculating the OR

<table>
<thead>
<tr>
<th>Case</th>
<th>Control</th>
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<tr>
<td>A</td>
<td>B</td>
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OR = \frac{AD}{BC}
What is a confounder

- a variable that distorts the results
- a confounder is a variable that:
  - Is associated with the outcome
  - Is associated with the exposure
- basically it causes a ‘mixing’ effect in the results of the study
Controlling for confounding

- How do we know the cases and controls are not different with respect to other variables?

- Example: Looking at the association between rofecoxib and myocardial infarction
  - What if the rofecoxib users are sicker?
Controlling for confounding

- restriction
- stratification
- statistical adjustment
Cohort studies

- by definition, group of people share similar characteristics followed forward
- some exposed, some unexposed
- at the end of follow up, rate of exposed compared to rate of unexposed
- using statistics, potential confounders is controlled for
Dynamic cohort

Cohort Entry: 2005
Time: 2005 - 2012
Bias in pharmacoepidemiology

- bias → Systematic error in research
- types of bias
  - recall bias → difficulty recalling drug
  - selection bias → one group different than another
  - channeling bias → drug prescribed to sicker patients
  - misclassification bias → Either disease or drug misclassified
Canadian administrative databases

- originally used for admin purposes
- Saskatchewan data used first for research
- 1980’s: Î number of pharmacoepi research
- late 1990s: data from Quebec, BC, Ontario used for research
- data access is challenging
Population Based Registries

Hospital

Medical

Home Care

Nursing Home

Pharmaceutical

Provider

Cost

Vital Statistics

Population - Based Research Registry
Advantages of admin data

- large N
- relatively fast access
- helps improve health services research
- helps shape health policy
- improves epidemiologic methods
- ideal for research on rare events
Examples of administrative databases

- administrative data in Canada
  - BCLHD
  - Ontario Linked Databases
  - RAMQ
  - Saskatchewan Linked Databases

- clinical databases
  - GPRD
  - MEMO database
British Columbia Linked Health Databases

- captures information on ~ 4.5 million residents
- data goes back as far as 1985
- most recent data 2011
Databases within the BCLHD

- PharmaNet
- hospital separation
- MSP
- births/deaths
- BC Cancer
- mental health
Disadvantages of administrative data

- validity questioned
- may take years to access data
- costs-up to hundreds of thousands of $
- data access-privacy
Clinical databases

- clinical databases - intended for clinical research
- include variables including
  - smoking status
  - alcohol intake
  - BMI
  - cholesterol
  - BP
- usually cost more than admin data
General Practice Research Database (GPRD)

- largest clinical database available
- based in the UK
- coding based on OXMIS not ICD-9
- Oxford Medical Information System
- captures information on
  - BMI, smoking, cholesterol, BP
Impact of pharmacoepidemiology

- population based drug related studies
  - rare drug adverse events
  - drug efficacy
  - drug interactions
  - patterns of use
“Side effects may include loss of appetite, job, home and family.”
The **Vioxx®** controversy

- first reports of MI in VIGOR
- confirmed by cohort study
- published in the Lancet
- 400K Medicaid patients
- 1 in risk of MI
Studying drug interactions in pharmacoepidemiology

- drug interaction studies
  - usually small human studies
  - in vitro studies
  - soft end-points

- usually look at soft outcomes

- clinical significance of interaction-unknown
  - cimetidine $\rightarrow$ P-450 inhibition
    - not all interactions clinically significant
Drug interactions in pharmacoepidemiology

- case-control study by Juurlink (JAMA; 2003)
- looked at interaction between
  - cotrimoxazole + glyburide → hypoglycemia
  - clarithromycin + digoxin → digoxin toxicity
  - K⁺ sparing diuretics + Ace-inhibitors → hyperkalemia
- used the ODB data using 1.5 million older adults
- 7 years time span
- matched for age, sex, medication, renal disease, comorb
Juurlink et al (JAMA, 2003)

Results

- Cotrimoxazole+glyburide  OR=6.6  (95% CI, 4.5-9.7)
- Clarithryomcin+digoxin   OR=11.7  (95% CI, 7.5-18.2)
- K+ sparing diuretics+Ace-I OR=20.3  (95% CI, 13.14-30.7)

Pharmacoepidemiology valuable tool in quantifying drug interactions
Statins and COPD mortality (Mancini JACC 2006)

- COPD
  - disease with high morbidity and mortality
  - inflammation-important role in the pathology of COPD
- statins-popular cholesterol lowering drugs
  - ↓ death secondary to CAD
  - may have anti-inflammatory properties
  - antioxidative properties
- study question: can statins lower the risk of COPD hospitalization/death?
Inflammatory and antioxidative effects of statins
Statins and COPD mortality (Mancini et al. JACC 2006)

- case-control study using Quebec data
- nested within cohort of subjects with CAD
- odds ratios statins
  - COPD hospitalization: 0.88 (0.69-1.12)
  - total mortality: 0.62 (0.48-0.79)
  - MI: 0.44 (0.36-0.54)
Impact of pharmacoepidemiologic studies on drug policy

- **Fen-Phen®**
  - JAMA
  - New Eng J Med
  - 1995

- **Zyprexa® (olanzapine)**
  - BMJ
  - 1998

- **Cipro® (ciprofloxacin)**
  - BMJ
  - 2002

- **Vioxx® (rofecoxib)**
  - Lancet
  - 2004

- **Tequin® (gatifloxacin)**
  - New Eng J Med
  - 2006
"And these blue ones are for the stomach cramps these red ones are going to give you."
Pitfalls of pharmacoepidemiology

- poly-pharmacy
- publication of poorly conducted studies
- misinterpretation of results by consumers
Pharmacoepidemiology programs in Canada

- most universities do not offer formal programs
- McGill University
  - formal program in pharmacoepidemiology
    - MSc/Ph.D
  - summer program → Certificate program
- Most universities don’t offer formal programs
  - Need to enter general Epid/Biostats program
  - Specialize in Pharmacoepidemiology
Pharmacoepidemiology programs in the US

- Boston Collaborative Drug Surveillance Program
- Center for Clinical Epidemiology and Biostatistics
  - university of Pennsylvania
- Brigham and Women Hospital
  - affiliated with Harvard