Observational Designs for Practice-Relevant Medication Use Research

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Outline
• Pharmacoepidemiologists specialize in using observational designs to answer practice-relevant medication use research questions.
• Observational research designs are uniquely suited to provide practice-relevant answers to medication use questions.
• The backlog of unanswered questions about medication effects in practice is enormous.
• The data and methods for pharmacoepidemiologic research may be reaching the tipping point.
  – Rigor of pharmacoepidemiology methods is stabilizing.
  – Might the methods be used in pharmaceutical public health practice?

Pharmacoepidemiology
• Strom (Pharmacoepidemiology, 4th ed)
  “Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people.”
• The observational study design, especially a retrospective cohort study “fielded” in an administrative database, is the work-horse of the pharmacoepidemiology discipline.

Limit of Premarketing Trials
• Carefully selected subjects may not reflect real-life patients in whom drug will be used
• Study subjects may receive better care than real-life patients
• Short duration of treatment
• Trials with 3000 patients cannot reliably detect adverse events with an incidence of < 1 per 1000, even if severe
• No info on comparative effectiveness

Thus….
• Premarketing studies cannot assure a positive balance of safety and effectiveness for chronic treatments
• Large numbers of heterogeneous subjects/patients must be evaluated for long periods of time
Medication Effects in the Elderly: RCTs vs. Observational Studies

Demographics of Subjects Enrolled in Two Observational Studies Compared with ECOG Cancer Trials

<table>
<thead>
<tr>
<th>Demographics</th>
<th>CanCORS SEER ECOG</th>
<th>CanCORS SEER ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Studies</td>
<td>Median age</td>
<td>68</td>
</tr>
<tr>
<td>% Age 75-85</td>
<td>20</td>
<td>27.9</td>
</tr>
<tr>
<td>% Age 86+</td>
<td>3</td>
<td>6.9</td>
</tr>
<tr>
<td>Colorectal Cancer Studies</td>
<td>Median age</td>
<td>66</td>
</tr>
<tr>
<td>% Age 75-85</td>
<td>18.3</td>
<td>29.2</td>
</tr>
<tr>
<td>% Age 86+</td>
<td>8.2</td>
<td>12.6</td>
</tr>
</tbody>
</table>

*CanCORS=Cancer Care Outcomes Research and Surveillance consortium; SEER=Surveillance, Epidemiology and End Results program.

Schrag et al, JNCI 2001

Receipt of Adjuvant Chemotherapy Stage III Colon Cancer

(n=6,262 SEER-Medicare)

Sample Pharmacoepidemiology Research Questions

- What factors in the physician-patient encounter influence treatment compliance and continuity of care?
- What system and healthcare environment characteristics influence the risk of prescribing errors?
- Why do so few elderly patients with stage III colorectal cancer receive chemotherapy?
- What is the comparative effectiveness of single agent vs. combination chemotherapy for octogenarian lung cancer patients?
- Are some antipsychotics safer than others?
- Are tissue ACE inhibitors more effective than non-tissue ACE inhibitors?

Rational Therapeutics

- “Given current knowledge, the best therapy to treat a health condition, balancing efficacy, safety, and cost.”

Define Impacts → Assess Use → Improve Practice

Safety, comparative effectiveness → Undesire, misuse, overuse → Programs: CPOE, Policies: Medicare, Drug Benefit

Aside: Need for Evidence-Based Quality Indicators

- Evidence deficit -
- RCTs of relevant questions (comparative effectiveness, drug-drug interactions, drug-disease interactions) sparse and sometimes unethical.
- Observational studies comparing effectiveness are still rare.
- Anecdotal reports contribute about 30% of the world literature on adverse drug reactions.
- Substituting “expert raters” for evidence often does not meet psychometric standards.
Disagreement Within Expert Panels

Intraclass correlation among expert raters

Evidence Ratings:
- Quantity of Evidence: 0.71
- Quality of Evidence: 0.65
- Causal Relationship: 0.60

Severity Ratings:
- Clinical Importance: 0.39
- Risk of Mortality: 0.32
- Risk of Morbidity: 0.26
- Likelihood of Intervention: 0.43

Probability of Interaction Ratings:
- Risk of Adverse Event: 0.16
- Timing of Medication: 0.16
- Importance of Age: 0.29
- Importance of Gender: 0.17
- Concurrent Diseases: 0.20

Might resources be better directed toward correcting the evidence deficit?

Primary Need for Pharmacoepidemiology

- Marketed drugs have documented efficacy. They prevent or mitigate disease and pain.
- But agents this powerful also have the power to alter some biological processes to our detriment.
- To do more good than harm, methods are needed to precisely estimate the net effects of medications in society.

Many Drugs, Much Uncertainty

- Limitations of pre-marketing clinical trials leave many questions unanswered:
  - Effects in unstudied population groups (elders, pediatrics)
  - Effects in combination with other drugs
  - Effects among individuals with co-morbid disease states
  - Effects in alternative dosages, dosage regimens
  - Effects over unstudied durations
  - Effects when used off-label
  - Net effects on dimensions of health
  - Low frequency effects

Discovery of drug effects in the population laboratory?

- 51% of drugs have label changes due to major safety issues discovered after marketing.
- 20% of drugs get new “black box” warnings after marketing
- 4% of drugs are ultimately withdrawn for safety reasons
- During 1999–2005, only 48% of new EU medicines had been studied in randomized comparisons with other active compounds.
The Need is Increasing

1. Increasing burden of disease
   a. Population aging and fattening
   b. Redefining disease thresholds
2. Accelerating pace of technology development
3. Financial limitations

Pharmacoepidemiology expertise may be reaching the tipping point.

Example of a Pharmacoepidemiology Study to Define Effects

When could we have suspected a link?

Rosfecoxib and myocardial infarction
HMO Research Network CERT – 7 million

- Relative risk rapidly stabilized between 1.5 and 2.
- 1500 observed events
- 25 breast cancer among women using drug.
- Would have required 200 or 3rd month if 100 million people had been observed.


Rigor of pharmacoepidemiology methods is stabilizing
Biases in Pharmacoepidemiology Studies

• Treatment selection bias ~ confounding
  – Randomization insures that there is no systematic difference between treatment groups
  – Observational (non-experimental) research there is no guarantee groups are similar
  – Receipt of treatment may be confounded
• Healthy user bias / adherence bias
• Differential surveillance for outcomes
• Selection bias due to informative censoring
  – Treatment discontinuation, switching

Advances in Pharmacoepidemiology Studies

• Addressing confounding
  – Active comparator drug used for other indication
  – Instrumental variables analysis
  – Propensity score calibration
• Addressing healthy user bias
  – New user designs
  – Matching on prior healthcare use
  – Avoid non-user comparators – enriched for people who are not health seeking.
• Addressing differential surveillance
  – Case definitions that will always be detected
• Addressing informative censoring
  – Intention-to-treat analysis

Confounding during treatment selection

• Prognostic data is used by physicians when they make treatment recommendations.
• If the prognostic variables used are independently related to an outcome being studied, then they are confounders.
• Failure to properly account for such variables can bias estimates of treatment effects.

Example

• Fluoxetine (Prozac) was the first SSRI-type anti-depressant
• Marketed as being safer and more effective than older antidepressants
• Reports of suicide and violent behavior among patients recently started on Prozac
• Confounding by disease severity?

Differential surveillance for outcomes

Drug user →
  Doctor visits to get prescriptions; monitoring for suspected ADEs; work-up of drug-induced benign symptoms
  → Increased detection opportunities

The “Healthy User” Bias / Adherence Bias

• Patients who initiate and are adherent to long-term preventive drug therapy are more health seeking. (Ray W, AJE 2000)
• Sample of prevalent users is over-sampling health-seeking patients
  – Exercise more, eat better, get regular check-ups
• They also are enriched for those who tolerate the treatment.
• Possible explanation for divergence between RCTs and observational studies
  – Hormone (replacement) therapy and CAD
  – Many surprising protective findings (Statins associated with a reduced risk of cancer, hip fracture, etc.)
patients are either steered towards drugs in order for them to benefit from their beneficial effect or steered away from them to avoid their harmful effects.
Using Multiple Design Approaches to Bound Effect Estimates

**Handling Treatment Discontinuation**

1. **Intention-to-treat**
   - Protect against bias from informative censoring
   - May result in severe bias toward null
   - Many drug effects can occur only when on drug

2. **Define exposed person-time and either**
   - Censor patients when they discontinue or
   - Allow treatment to be time-varying (e.g., patients can cross-over into other "treatment arms")

Defining Study Endpoints

- For studies with variable follow-up time, censoring events must be defined:
  - first of death, end of follow-up, study event, treatment discontinuation
- Outcome definition
  - Case definition with acceptable sensitivity and positive predictive value.
- Medical record access to confirm case diagnosis

Problems with Overall Mortality as a Study Endpoint

- Nonspecific
  - Ex. Coxib effect on cardiovascular death may be swamped by including all-cause mortality
- Controlling for confounding variables is particularly difficult.
- Illnesses that precede death may alter drug use (reverse causality).

Unmeasured Confounding in Claims Data

- Database studies are criticized for their inability to measure clinical and life-style variables that are independent predictors of the study outcome
  - OTC drug use
  - BMI
  - Clinical variables: Lab values, blood pressure, x-ray results
  - Physical functioning, ADL
  - Cognitive status
Analysis
Approaches

• Measured confounders
  – Sensitivity analysis with increasing restriction
  – Stratification
  – Multivariate outcome models
  – Propensity score adjustment
• Unmeasured confounders
  – External adjustment (regression calibration)
  – Instrumental variables

Translating pharmacoepidemiology methods into good pharmaceutical public health practice

Job Description for a Pharmaceutical Public Health Practitioner

(i) identify health-related community problems;
(ii) set health priorities;
(iii) formulate policy and make decisions;
(iv) perform management and administrative functions;
(v) educate the community to recognize, and cooperate in serving, its health needs;
(vi) advise, consult, and support community service programs, and
(vii) perform research and/or evaluate activities in public health.

It is easy to see how a pharmacist working at a macro e.g. health plan level would perform all of the above – with a focus on medication use and effects.

Conclusion

• Observational research designs are uniquely appropriate for defining the effects of drugs in community care.
• Resources invested identifying and quantifying medication effects in practice will bolster the quality of our measures of underuse, misuse, and overuse. In turn, such measures, or quality indicators, are important metrics for evaluating interventions to improve practice.

Define Effects  →  Assess Use  →  Improve Practice

Safety, comparative effectiveness  →  Underuse, misuse, overuse

Programs: CPOE, Medicare Drug Benefit