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Measure Error or Harm?

- Error
  - Evaluate effectiveness of system changes
    - Implementation of bar-code system
      - Near miss vs. Reached the patient
        - Direct observation - Not captured with trigger tool
- Harm
  - Evaluate treatment pathway
    - Coumadin management
      - Identify harm regardless of error

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Common Study Design Considerations

- Pre-Post (Quasi-experimental)
  - 1-group pretest-posttest design
    - May be difficult to control for confounding
      - Variables may differ between the two periods
        - demographic, clinical, system
    - Results may be a result of regression to the mean
      - Trigger for many interventions is rise in rate above normal
    - Maturation effects
      - Participants become more experienced, wiser, more skillful over time
    - Seasonal effects

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Common Study Design Considerations

- Parallel Comparator Group – single measurement
  - Threat from time related changes is reduced
    - Seasonality
    - Maturation
  - Possibility for Selection Bias and Confounding
    - Culture of safety and systems differences likely exist

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Other Designs

- Cluster Randomization
- Quasi-experimental designs that use control groups and pretests

  I1 X I2 Evaluate change in control group

  C1 C2 *Intervention must not yet be in place
- Practice Based Evidence Design
  - Providers identify important characteristics
  - Documentation becomes part of everyday practice

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Confounding

Occurs when the apparent association between a risk factor and outcome is affected by the relationship of a 3rd variable

1. A risk factor for the disease
2. Associated with the exposure of interest
3. Can not be an effect of the exposure
   - Cannot be on the causal pathway
     - Diet → Cholesterol Levels → MI

Katz MH. Multivariable Analysis. *Ann Intern Med.* 2003;138:644-650.

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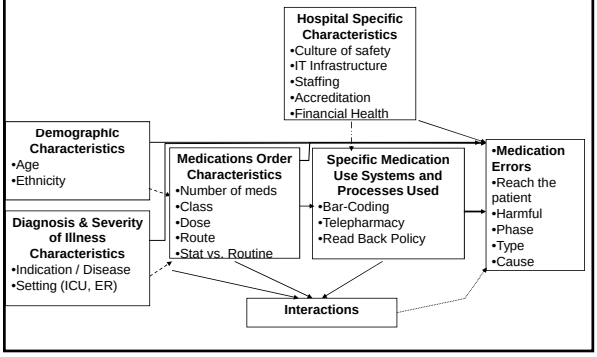
Potential Confounders



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Methods to Control for Confounding

- Randomization
  - Reduces likelihood of confounding
  - Difficult if not impossible
    - Patients, Providers, Units, Hospitals
- Matching
  - Patient characteristics
  - System characteristics
- Exclusion
- Statistical control for confounding - Regression

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Sample Size Considerations

- Errors are rare events
- Logistic & Proportional Hazards regression – 10 outcomes for each independent variable
  - Based on the less frequent state of the dichotomous outcome
    - 1000 people in study, only 6 develop disease

Katz MH. Multivariable Analysis. *Ann Intern Med.* 2003;138:644-650.

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Analyzing Correlated (Clustered) Data

- Observations may be correlated:
  - Patient, Provider, Unit, Hospital
- If uncorrected, the standard errors of the estimates will be off (usually underestimated)
  - Each observation contains less unique information
- Intraclass correlation should be evaluated and the regression model adjusted if necessary

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Conclusions

- Clearly define the study's purpose and outcome of interest.
- Study designs and threats to validity are similar to clinical research.
- Consider sample size when evaluating feasibility

Using Automated Data for Medication Safety Research

Dan Hartung, Pharm.D., MPH
Assistant Professor – Pharmacy Practice
Oregon State University – College of Pharmacy
Oregon Health & Science University – Department of Medical Informatics and Clinical Epidemiology

Disclosures

- Career Development Award – Comparative Effectiveness Research
  - K12HS019456-01
- Sedative Hypnotic use by the mentally ill: a Medicaid prescription policy study
  - CoI: R01MH086310-03

Educational Objectives

1. Understand the strengths and limitations of using existing healthcare databases for conducting medication safety research
2. Describe different methodologic approaches for conducting medication safety research
3. Be able to calculate and interpret measures of association appropriate for differing study designs
4. Be familiar with basic approaches for dealing with issues of bias and confounding in observational research of medication safety

Medication Safety

- Injury caused by medical management is 4th to 8th leading cause of death
- Medications largest single category contributing to adverse events (1 in 5)
- 25% are preventable

1998

Some Nomenclature

- **Adverse event:** harmful or undesirable outcome that occurs during or after the use of a drug (or intervention) but is not necessarily caused by or
  - defined as an injury caused by medical management rather than by the underlying disease or condition of the patient
- **Adverse effect:** harmful or undesirable outcome for which there is at lease a reasonable possibility of a causal relation
- **Medication error:** Failure of a planned action to be completed as intended or use of a wrong plan to achieve an aim
- **Adverse reaction (ADR):** an adverse effect specifically associated with a drug
- **Harms:** generic term used to refer to the totality of all possible adverse consequences of an intervention

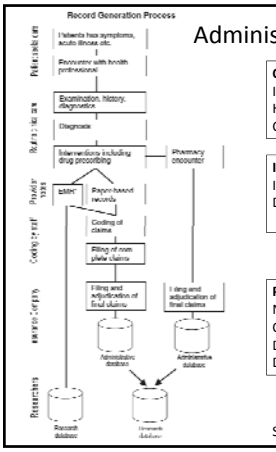
Challenges in Assessing Harms

- Studies, particularly trials, often designed to assess benefits
- Many harms may be unknown prior to design
- Many harms may require long term follow-up to ascertain
- Efficacy studies may underestimate "real world" harms (magnitude, frequency)

Automated Data Sources

- Administrative Data – generated for payment of healthcare services
- Electronic Health Records – computerized medical records
- Registries
  - Organized system that uses observational study methods to collect uniform data
  - population defined by a particular disease or exposure
  - population defined by a particular disease or exposure

Administrative Data



Outpatient
ICD9 diagnostic codes
HCPCS codes ~ procedure codes
Clinical administered drugs (J codes)

Inpatient / Hospitalizations
ICD9 Codes
DRG Codes

Pharmacy
NDC
Quantity dispensed
Day supply
Date

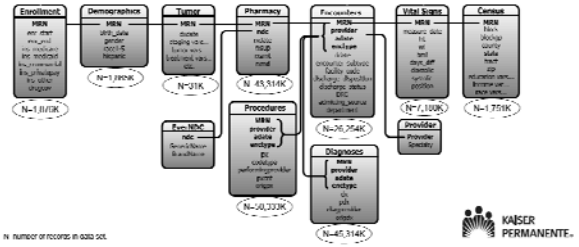
Schneeweiss S, et al J Clin Epidemiol 2005;58:323-37

Administrative Data

Advantages
- Low cost??
- Large sample size
- Timely
- Real-world documentation
- Recall biases less problematic
- Pharmacy data historically very accurate of consumption
  - impact of $4 generic programs???

Limitations
- NOT built for research
- Coding validity questionable
  - Outcome validity
- Important clinical variables missing (smoking, weight)
- Generalizability limited to source population

Electronic Health Records



Electronic Health Records

Advantages
- Low cost??
- More clinically important variables
- Larger sample size
- Timely
- Real-world documentation
- Recall biases less problematic
- Pharmacy data typically reflects written prescriptions (not filling)
  - Abandoned Rx phenomena

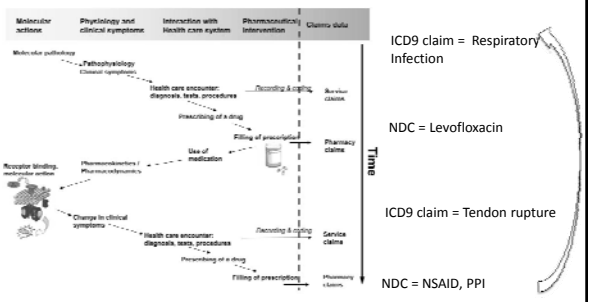
Limitations
- NOT built for research
- Coding validity questionable
- Important clinical variables missing (smoking, weight)
- Generalizability limited to source population
- May be missing some data from outside clinicians
- Depending on structure some while present may not be easily accessible

Hybrid Sources

DARTNet
Informing Practice Improving Care

- Network of >200 primary care clinicians using disparate EHRs
- Captures >150 data elements from clinical and administrative sources
- Bidirectional capacity for POC data entry

Administrative Data: Real world proxies for health outcomes



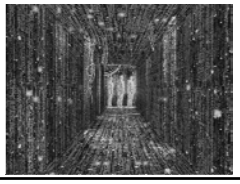
Schneewiss S, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.

Unraveling the Code

MRN	Sex	Race	DOB
547895	F	M	4/3/56

MRN	NDC	Quantity	DaySupply	FillDate
547895	4565648412	31	31	7/30/10
547895	0064234865	30	30	8/31/10
547865	4597215911	31	31	10/1/10

MRN	CPT	Dx1	Dx2	Dx3	Dx4	Dx5	DRG	Date
547895	99201	25006	2954					7/15/10
547895	999211	25006	413					8/30/10
547865	99211	413	25002					9/15/10
547865	83036	2500						9/15/10
547865		410	250006				110	10/2/10



A 55 yo male
-3 fills for rosiglitazone
-2 outpatient visits for type 2 DM
-1 outpatient visit for angina with a lab claim for HbA1c
-1 hospitalization for AMI

Unraveling the Code

- Pharmacy – National Drug Code (NDC)
  - 11 digit code that IDs drug product, package size, manufacturer
  - Several proprietary sources: First DataBank, Medi-Span
  - Public sources: VA National Drug File, NLM – RxNorm

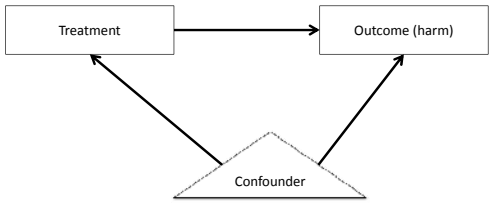
Unraveling the Code

- Procedure Codes (CPT)
  - 5 character codes that providers submit in order to be paid for a service rendered
  - Maintained by AMA
- ICD9 Diagnostic Codes
  - 5 character code which identifies diagnoses that care is directed for
  - http://www.cdc.gov/nchs/icd/icd9cm.htm

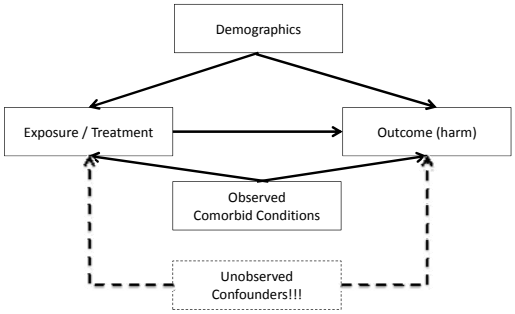
Administrative Claim Sources

- Medicaid
  - State / locally acquired
  - CMS Medicaid Analytic Extract (MAX)
- Medicare
  - Research Identifiable Files
- IMS
  - PharmMetrics® Largest non-payer owned claims database of commercial insurers in the US
  - IMS prescription data – 73% of total prescription activity across commericial, Medicare, Medicaid

Clinical Epidemiology – Conceptual Model



What we're up against



Is an Association Real??

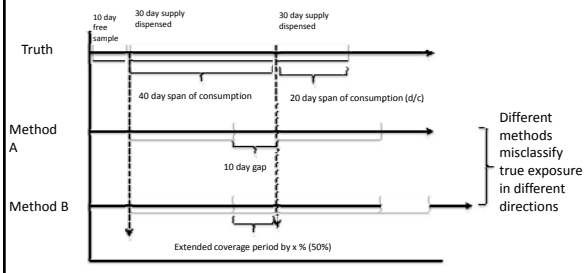
1. Bias
2. Confounding
3. Chance
4. True Association!!!

-Is it causal?? – other observations, biologic plausibility, magnitude

Defining outcomes and exposures

- Outcomes
  - Incident diseases identified through ICD9 coding
  - +/- service delivered in hospital or ED
- Exposures
  - Drugs identified through NDC system
- Other variables
  - Comorbid diagnosis of interest
  - Relative severity of illness (many exist)

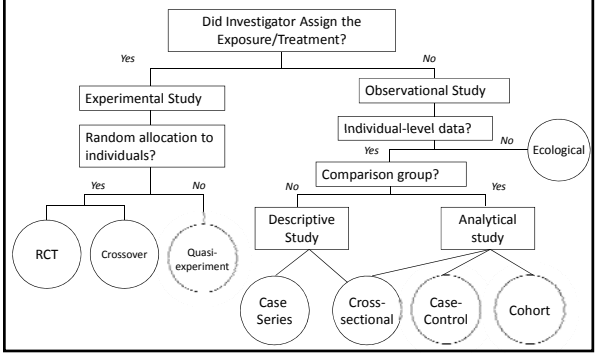
Defining Exposures



Defining Outcomes

- Basic measures
  - ED visits
  - Hospitalizations
- Specific measures
  - Diagnostic coding for specific conditions may have variable sensitivity and specificity
  - Validation of outcome coding preferable

Methodologic Approaches



The Epidemiologists' World View

Cohort Studies

Case-Control

	Disease (outcome)	No Disease (outcome)	
Exposure (Treatment)	A	B	A+B
Not Exposed (No Treatment)	C	D	C+D
	A+C	B+D	N=A+B+C+D

Cohort Studies

- Group of subjects
- Followed over time
- Exposures (rx use) of subjects assessed
- Outcome of interested observed

N=100 Treated with Drug A → 20 subjects have AMI
(t_0 to t_x)

N=100 Treated with Drug B → 40 subjects have AMI
(t_0 to t_x)

Cohort Studies

Treated with Drug A
Treated with Drug B

Prospective

- Investigator prospectively collects data from subjects
- Allows detailed assessment of important exposures
- Expensive (RCT is similar to prospective cohort study)

Retrospective

- Investigator uses an existing data
- All events and exposures have occurred
- Cohort is virtually constructed and followed forward through time
- Much less costly
- Limited control over exposure and outcome measurements

Retrospective Cohort Studies

Strengths

- Typically can be very large at relatively low cost
- Multiple outcome assessment possible
- Time sequence for causality more defensible
- **Directly calculate incidence (risk) ~ Risk Ratio**

Limitations

- Difficulty for rare events
- Exposure assessment limited
- Ascertainment of exposures and outcomes for retrospective studies can be suspect

Example: COX2 inhibitors and GI Events

- Setting: Pennsylvania Medicare program
- Cohort: initiators of NSAID versus selective COX2 inhibitors (1991-2002). No use in the prior 18 months
- Patients followed for 18 months after initiation
- Outcomes: (hospitalization for GI hemorrhage or PUD

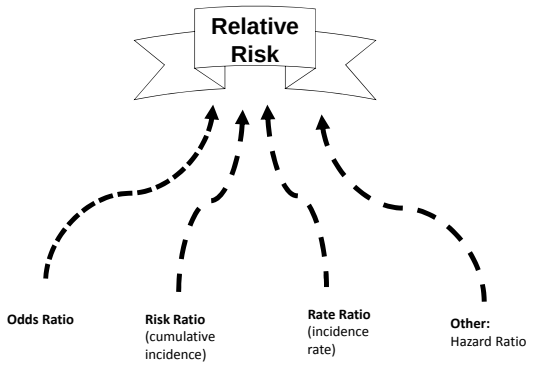
Schneewiss S, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.

Example: COX2 inhibitors and GI Events

Cohort Studies

	GI Event	No GI Event	
COX2 inhibitors	367	31,675	32,042
NSAIDs	185	17,426	17,611
	552	49,101	49,653

Cumulative incidence (Risk) of GI event:
COX2 inhibitors: 367 / 32,042 = 1.14%
NSAIDs: 185 / 17,426 = 1.06%



Example: COX2 inhibitors and GI Events

Cohort Studies

	GI Event	No GI Event	
COX2 inhibitors	367	31,675	32,042
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	552	49,101	49,653

Cumulative incidence (Risk) of GI event:
COX2 inhibitors: 367 / 32,042 = 1.14%
NSAIDs: 185 / 17,426 = 1.06%

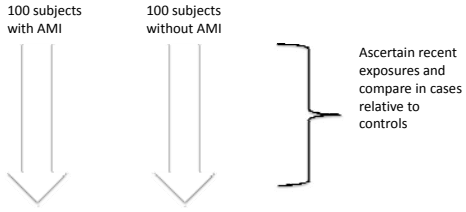
Risk of GI event in COX2 inhibitors relative to NSAID users = 1.14% / 1.06% = 1.08

The risk of GI event is 1.08 times higher among COX2 inhibitor users relative to NSAID user

Huh???

Case-Control

- **Study subjects defined by outcome of interest**



Case-Control Example

- Setting: Saskatchewan administrative data
- Cases: upper GI complication
- Control: randomly selected patients with adequate eligibility*

Castellsague J, et al. Risk of Upper Gastrointestinal Complications Associated with Cyclooxygenase-2 Selective and Nonselective Nonsteroidal Antiinflammatory Drugs. Pharmacotherapy. 2009:29:1397-07

Case-Control Example

Case-Control

	GI Event	No GI Event	
COX2 Use	90	307	397
No COX2 Use	636	19,695	20,331
	726	20,002	20,728

Incidence or risk CANNOT be directly calculated because case distribution is artificially constructed

We CAN calculate **Odds of Exposure of Cases and Controls**
-- **Odds Ratio (OR)** is an estimate of underlying **Relative Risk**

Probabilities vs. Odds

If we roll a die, we could get any number, 1-6, with equal likelihood

We've rolled a 3.

We could've rolled: 1,2,4,5,6

$$P(\text{rolling a 3}) = 1/6 = \frac{\#\text{ outcomes of interest}}{\text{Total \# of possible outcomes}}$$

$$\text{Odds(rolling a 3)} = 1/5 = \frac{\#\text{ outcomes of interest}}{\#\text{ of alternate possible outcomes}} = \frac{P(\text{rolling a 3})}{1\text{-}P(\text{rolling a 3})}$$

Note:
$0 \le P \le 1$
$0 \le \text{Odds} \le \infty$
Odds > P

Odds

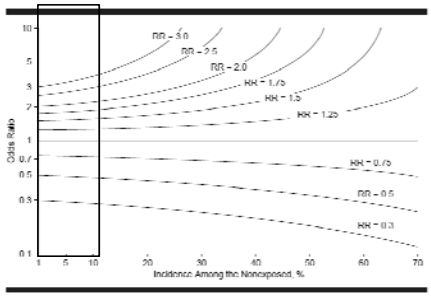
	GI Event	No GI Event	
COX2 Use	90	307	397
No COX2 Use	636	19,695	20,331
	726	20,002	20,728

Odds of exposure among cases = 90 / 636 = 0.142
Odds of exposure among controls = 307 / 19,695 =0.016

Ratio of odds of exposure among case relative to controls = 0.142/0.016 = 9.08

Using OR as an estimate of Relative Risk, the risk of GI event is 9 fold higher among COX2 users relative to non-users

OR is a good estimate of RR when overall incidence is low (<10%)



The relationship between risk ratio (RR) and odds ratio by incidence of the outcome.

Zhang... What's the Relative Risk? Zhang & Yu

The Odds Ratio

- Can be calculated for:
  - Case-control studies
  - Cohort studies
  - +/- cross-sectional ~ debatable (interpretation is different)
- As a product of many multivariate statistical models
  - Crude/unadjusted versus adjusted ORs

Case Control

Advantages

- Efficient for rare events
- Can assess multiple exposures (potentially useful for generating hypotheses on many exposures)
- Lower cost (relative to prospective cohort)

Limitations

- Limited to one outcome
- Cannot directly calculate incidence (risk)
- Highly susceptible to various biases
  - Recall
  - misclassification

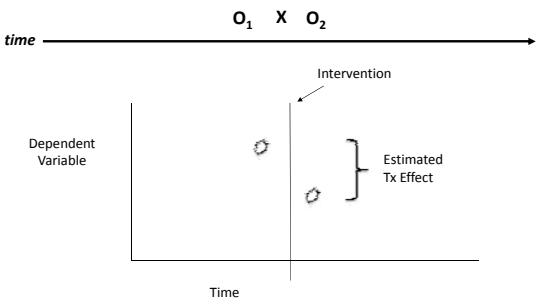
Selecting Controls

- Must be representative of the **source population of cases**
  - If a control subject developed a case condition they would likely be included as a case
  - Should be comparable to cases with respect to baseline risk of developing condition and completeness of data
- Common control sources
  - Population sample
  - Similar-system user controls
  - Self-control (more later)
- 4 controls per case

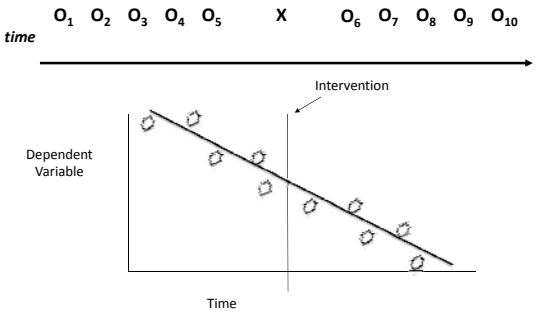
Quasi-Experiment

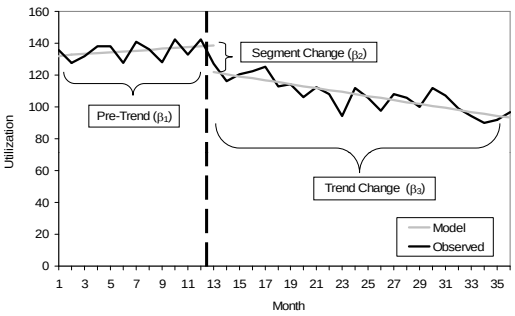
- Non-randomized experiments where people are assigned (at the group level) to an intervention
  - State law
  - Rx Policy
  - Broadly implemented pharmacy program
  - Program to reduce ADRs/errors
- **Also** In theory, group assignment should not be associated with likelihood of outcome of interest but strongly associated with intervention of interest
  - Instrument for sorting subjects

Pre-Post Design

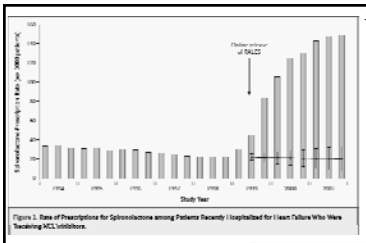


Pre-Post Design

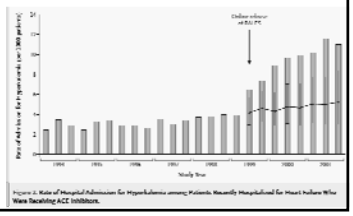




Juurlink DN, et al. NEJM 2004;351:543-51



- Increasing use of spironolactone after RALEs study in patients HF associated with increase ADR for hyperkalemia
- Use of spironolactone likely causes hospitalization for hyperkalemia
  - Unlikely to be alternative explanation



Quasi-Experiment

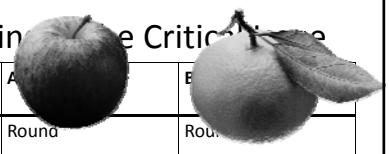
Advantages

- Take advantages of natural experiments
- Can possibly use to control for unmeasured explanations (confounding) – Instrument
- Individual level data not used

Limitations

- Need natural experiment
- Secular changes in other important co-variates
  - Concurrent policies

Confoundi e Critic e



	A	B
Shape	Round	Rou
Source	Tree	Tree
Edible?	Yes	Yes
Size	Handheld	Handheld
Weight	½ pound	½ pound

Dealing with Confounding

- Confounding by indication (channeling bias) is the fundamental challenge for observational research
  - Effectiveness Research – can be fatal flaw
  - Harms Research - might be workable if harm is relatively unknown
- Administrative data often lack detailed information on critical variables
  - Fragility
  - Severity of disease

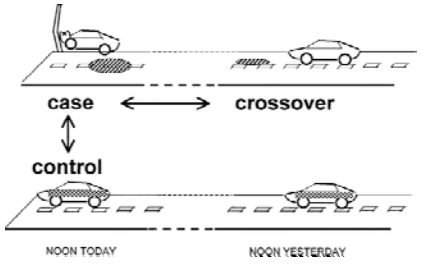
Controlling for Confounding

- Matching
- Restriction / stratification
- Statistical Adjustment
  - Multivariate regression (logistic , linear)
  - Cox proportional hazards
- Advanced methods
  - Propensity score – alternative balancing technique
  - Instrumental variables – unmeasured confounding?

Case-Crossover Design

- Hybrid design to evaluate the immediate causes of an outcome
  - "was event triggered by something unusual just prior"
- Case services as its own control at different time
- Ideal for acute events and transient exposures
  - Viagra and CV events
- Because subjects serve as own control stable covariates (both measured and unmeasured) are inherently controlled
- Confounding can still occur for time-related changes in severity of disease

Case-Cross Over
Cell phone use and MVA

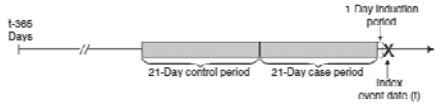


Maclure M, Mittleman, MA. Annu Rev Public Health 2000 21:193-221

Refilling and Switching of Antiepileptic Drugs and Seizure-Related Events

JJ Gagne[1], J Avorn[1], WH Shrank[1] and S Schneeweiss[1]

- Goal – to quantify the risk of seizure-related events associated with refilling an Rx for the same AED from same manufacturer and estimate the additional risk associated with switching between AED manufactured by different companies (e.g. Brand to Generic switching)
- Case period 21 days prior to index event
- Control period 21 days immediately preceding the case period



Gagne JJ, et al. Clinical Pharmacology and therapeutics. 2010;88:347-53.

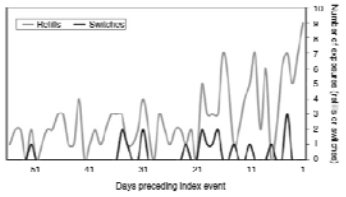


Figure 2 Distributions of exposures (refills and switches) in the 8 weeks preceding the index event dates.

Table 2 Odds ratios (95% CIs) for the association between antiepileptic prescription refilling and switching and incidence of seizure-related outcomes for primary analyses

No. of days in case/control periods	Refill of prescription for the same drug, strength, and dosage form from the same manufacturer[a]		Switch to a different manufacturer of the same drug, of the same strength and dosage form[b]		Refill-adjusted odds ratio for switching
	n[c]	Odds ratio (95% CI)	n[c]	Odds ratio (95% CI)	Odds ratio (95% CI)
21	116	2.31 (1.56–3.44)	15	2.75 (0.88–8.64)	1.19 (0.35–3.99)
28	151	2.08 (1.48–2.93)	19	2.17 (0.82–5.70)	1.04 (0.37–2.90)

Gagne JJ, et al. Clinical Pharmacology and therapeutics. 2010;88:347-53.