Introduction to pharmacoepidemiology
Definitions, study designs, validity, and data sources

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Learning objectives
This course will provide an introduction to:
- Definition and applications of epidemiologic and pharmacoepidemiologic research
- Definitions, strengths, and limitations of main pharmacoepidemiologic study designs
- Concepts of internal and external validity of pharmacoepidemiologic studies
- Important data sources in pharmacoepidemiology

Course outline
1. Definitions & applications
   - Epidemiology & pharmacoepidemiology
2. Overview of study designs in pharmacoepidemiology
   - Randomized controlled trials vs. observational studies
3. Validity of pharmacoepidemiologic studies
   - Internal validity (bias)
   - External validity (generalizability)
4. Data sources in pharmacoepidemiology
   - Field studies
   - Administrative databases
1. Definitions & applications
   - Epidemiology
   - Pharmacoepidemiology

Epidemiology

Definition
- Study of the distribution and determinants of diseases in human populations (Rothman, 2002)
- Application of this knowledge for the prevention and management of diseases

Complex collection of research methods and statistics
Some applications

- Chronic diseases
- Infectious diseases
- Pharmacoepidemiology
- Clinical epidemiology
- Environmental epidemiology
- Screening
- Surveillance
- Reproductive and perinatal epidemiology
- Genetic epidemiology
- Nutritional epidemiology
- Economic evaluation & pharmacoconomics
- Occupational epidemiology
  ...and many more

Pharmacoepidemiology

**Definition**

- Study of the use and the effects of drugs in large number of people (MacMahon, 1970)
  - pharmacology → study of the effect of drugs
  - epidemiology → study of the distribution and determinants of diseases in populations

Pharmacoepidemiology

**Why pharmacoepi research?**

- To supplement information of premarketing studies with postmarketing studies
- To Study drug use and effects in uncontrolled real-life settings
### Pharmacoepidemiology

#### Drug development and approval process

<table>
<thead>
<tr>
<th>Premarketing studies in humans</th>
<th>Postmarketing studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug discovery</strong></td>
<td><strong>Development</strong></td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>Clinical</td>
<td>Phase 0</td>
</tr>
<tr>
<td>Phase I</td>
<td>Phase II</td>
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<tr>
<td>Phase III (Phase III studies, experimental studies)</td>
<td>Approval</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>Phase IV</td>
</tr>
</tbody>
</table>

(Adapted from Keiser et al., Trends in Parasitology, 2001)

### Pharmacoepidemiology

#### Premarketing human studies

- Randomized controlled trials (RCTs)
- Mandatory in the drug approval process
- Strict selection criteria, limited size, limited follow-up length

**Drug use and effects in ideal conditions**

( measure efficacy)

### Pharmacoepidemiology

#### Postmarketing studies

- Observational studies (Phase IV studies, pragmatic studies)
- Larger sample sizes and longer follow-ups
  - Rare and long-term drugs’ adverse events
- Patients not included in premarking studies
  - Pregnant women, children patients with many comorbidities/ polymedication, etc.

**Drug use and effects in real-life clinical settings**

( measure effectiveness)
Pharmacoepidemiology

Postmarketing studies
- Observational studies (Phase IV studies, pragmatic studies)
- Larger sample sizes and longer follow-ups: Rare and long-term adverse events
- Patients not included in premarketing studies: Pregnant women, children with many comorbidities/polymedication, etc.

Drug use and effects in real-life clinical settings (measure effectiveness)

What do we study?

Drug use
- Prevalence of use
- Patterns of use
- Determinants of use
- Who? When? Where?
- Persistence and adherence
- Prescription patterns

Drug effects
- Risks and benefits:
  - Effectiveness (real-life)
  - Safety (adverse events)
  - Satisfaction with treatment
  - Costs and consequences (pharmacoeconomics)

Complex collection of research methods and statistics

What is a risk?
- Measure of an effect
- Probability → possibility of suffering harm or loss, experiencing a good outcome
- Examples in pharmacoepi:
  - The probability of developing a disease, experiencing an adverse event, dying from a specific cause, being prescribed a medication, stopping a drug, etc.
Pharmacoepidemiology

Basic frequency & association to estimate risks

<table>
<thead>
<tr>
<th>Frequency measures</th>
<th>Measures of association between the exposure and the outcome</th>
<th>Study designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence (Risk)</td>
<td>Relative Risk (Risk among exposed/Risk among unexposed)</td>
<td>Randomized controlled trials &amp; cohort studies</td>
</tr>
<tr>
<td>Number of new cases/Number of persons initially at risk</td>
<td>Rate Ratio (Incidence rate among exposed/Incidence rate among unexposed)</td>
<td>Randomized controlled trials &amp; cohort studies</td>
</tr>
<tr>
<td>Incidence rate (Number of new cases/amount of at-risk experiences/person-time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes, calculation of incidence or incidence rate among exposed and unexposed subjects is impossible</td>
<td>Odds Ratio (Odds of exposition among cases/Odds of exposition among controls)</td>
<td>Case-control studies</td>
</tr>
</tbody>
</table>

2. Study designs
Randomized controlled trials vs. observational studies

Overview of epidemiologic study designs

- Randomized controlled trials (RCTs)
- Observational studies
  - Cohort studies
  - Case-control studies
- Cross sectional studies
- Pharmacoeconomic studies
- Descriptive studies
- Validation studies
- Quasi-experimental studies
- Ecologic studies

Advanced designs
- Nested case-control studies
- Case-crossover studies
- Case-cohort studies
- Case-time-control studies
Randomized controlled trials (RCTs)

- Premarketing phase III studies
- Experimental studies

- Used to evaluate efficacy and safety of treatments among humans
- Study subjects are randomly allocated to receive the treatment of interest or to serve as a control and then followed prospectively to compare their outcomes
- Mandatory in the drug approval process
- Drug use and effects in ideal conditions (efficacy)

Particularities and strengths of RCTs

1) Randomization
2) Control group
3) Blinding (when possible)
Randomization

- Random allocation of treatments
  - Experimental group
  - Control group
- Each subject have the same chance to be part of one group or another
- Randomization:
  - Assures the comparability of study groups
  - Assure that is a difference is found regarding treatment outcomes, it can be attributable to the treatment only
  - Minimize confusion

Particularities and strengths of RCTs

1) Randomization
2) Control group
3) Blinding (when possible)

Control group

- Essential to demonstrate that an effect is attributable to the treatment and not to a placebo effect, medical follow-up effect or time effect
Particularities and strengths of RCTs

1) Randomization
2) Control group
3) Blinding (when possible)

Blinding

- To insure that study outcomes are measured in the same way between exposed and non-exposed subjects (objective evaluation)
  - Single-blinded: Study subjects are not aware of their treatment
  - Double blind: Neither the study subjects nor the experimenter is aware treatment allocation

Impact of blinding on self-reported improvement following acupuncture for the management of low-back pain

Source: www.medicine.ox.ac.uk/bandolier/band80/b80-2.html

Example

Impact of blinding on self-reported improvement following acupuncture for the management of low-back pain

Source: www.medicine.ox.ac.uk/bandolier/band80/b80-2.html
Randomized controlled trials

- RCTs are actually the accepted gold standard for the evaluation of treatments and interventions
- According to many...
  "If you find that a study was not randomized, we'd suggest that you stop reading it and go on to the next article" (Benson & Hartz, NEJM, 2000)

Randomized controlled trials

- The hierarchy of medical evidence

<table>
<thead>
<tr>
<th>Quality</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meta-analysis of RCTs without significant heterogeneity</td>
<td>RCTs</td>
<td>Prospective cohort studies</td>
<td>Case-control studies</td>
<td>Retrospective cohort studies</td>
</tr>
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Randomized controlled trials

However....

Efficacy in ideal conditions (efficacy) vs.
Efficacy in real-life clinical setting (effectiveness)
Limits of RCTs

1) Strict selection criteria
   • Homogeneous and specific study populations
   • At low risk of developing complications (no comorbidities)
   • Motivated and adherent patients
   • Systematic and intensive follow-up, i.e. ideal clinical practice
   • Underrepresentation of some populations, i.e. pregnant women, children, etc.

   Capacity to generalize study results to the complex context of the real clinical practice?

Example 1
A study evaluated the characteristics of patients suffering from chronic diseases in the community and compared them to selection criteria of large RCTs studying the efficacy of treatments for the management of these health conditions

Only 0-36% of them would have been eligible

Example 2
Efficacy of pregabalin in patients with fibromyalgia

A 14 week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia

Lesley M. Arnold,†† I. Jon Russell,‡ H. W. Chin,‖ M. A. Raichle,‖ James P. Young,‖iatrics
Ulrike Sharma,‖ Susan A. Math,‡ Kenneth A. Berrett,‡ and George Nag"
Limits of RCTs

Example 2 (continued)

2) Length of follow-up in RCTs

- Short-term evaluation of drug efficacy and safety
- Not suitable for the detection of and long-term drugs’ adverse events

3) Ethical problems

- We cannot randomize patients to receive alcohol, tobacco, drugs, etc.
Observational studies

- Postmarketing phase IV studies
- Pragmatic studies

- Used to evaluate effectiveness and safety of treatments among humans in real-life clinical settings
- The researcher do not control the exposures of patients
  - No randomization
  - Exposures are not distributed at random
- Not placebo controlled (we compare to usual treatments)
- Standard of care
- We observe what is going on

Particularities and strengths

1) Broader selection criteria
   - Study of risks and benefits of drugs in populations who are excluded from premarketing RCTs
     - Pregnant women, children patients with many comorbidities/ polymedication, etc.
   - Real-life clinical practice and drug use context
   - ↑ capacity to generalize the study findings

Particularities and strengths

2) Larger sample sizes and longer follow-up periods
   - Rare and long-term drugs' adverse events
Observational studies

- Basic study designs
  - Cohort studies
  - Case-control studies
  - Cross sectional studies

Advanced designs
- Nested case-control studies
- Case-crossover studies
- Case-cohort studies
- Case-time control studies

Subjects are selected according to their exposure
Incidence of study outcomes over time is then compared between study groups

Cohort studies

- Subjects are selected according to their exposure
- Incidence of study outcomes over time is then compared between study groups

Strengths
- Measurement of risks over time
- We know that the exposure precedes the outcome (causal relationships)
- Many outcomes can be studied at the same time
- Study of rare expositions
- Time-to-event analysis is possible

Limits
- Expensive
- Not efficient for the study of rare outcomes
- Many bias associated to observational studies (especially confusion)

Cohort studies
Case-control studies

- Subjects are selected according to their outcome (cases vs controls) rather than exposure
- Previous exposures are then compared between cases and controls

### Evaluation of various exposures

**Odds Ratio**

- **Cases**: Experienced the outcome of interest
- **Controls**: Did not experience the outcome of interest

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**Case-control studies**

- **Example**: Impact of the duration of antidepressant use during pregnancy on the risk of major congenital malformations in offspring of women diagnosed with psychiatric disorders
  - **Cases**: Mothers of babies that were diagnosed with at least one major congenital malformation (ICD-9 codes)
  - **Controls**: Mothers of babies that were not diagnosed with any congenital malformation
  - **Exposure**: Exposure to antidepressants during the 1st trimester of pregnancy

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**Case-control studies**

- **Strengths**
  - Study of rare outcomes
  - Study of long-term outcomes in a more efficient way
  - Cheap, easy and quick as compared to field cohort studies
  - Many exposures can be studied at the same time

- **Limits**
  - Measurement of risks over time NOT possible
  - The Odds Ratio estimate the Relative Risk if the outcome is rare
  - Difficult to find controls who are comparable to cases
  - We are not always sure that the exposure preceded the outcome (affects the ability to identify causal relationships)
  - Many bias associated to observational studies (especially confusion)
Advanced designs in pharmacoepi

Efficient variants of the case-control design

- Nested case-control studies
- Case-crossover studies
- Case-cohort studies
- Case-time-control studies

Cross-sectional studies

- Subjects according to their exposure or outcome at a point in time
- No follow-up over time

Evaluation of various exposures and outcomes at the same time

Strengths

- Cheap, easy and quick
- Study of rare outcomes
- Study of long-term outcomes
- Many exposures or outcomes can be studied at the same time

Limits

- Less robust than every other observational designs
- We are not always sure that the exposure preceded the outcome (affects the ability to identify causal relationships)
- Measurement of risks over time NOT possible
- Many bias associated to observational studies (especially confusion)
4. Validity of studies
- Internal validity (bias)
- External validity (generalizability)

Validity of studies
• To be valid, pharmacoepidemiologic studies must have:
  1) Internal validity
     – Least possible bias
  2) External validity
     – Capacity to generalize the study findings

Internal validity
• The internal validity of epidemiologic studies can be affected by random error and systematic error

  1) Random error
     • Related to the variability of data, i.e. precision in assessing a given exposure-outcome association
     • It’s why we use statistics!
     • Can be minimized by increasing the size of the study
Internal validity

2) Systematic error

• Bias
• Systematic errors that arise because of the way the subjects are selected, the way variables are measured or the absence of control of confounding factors
• Bias can appear at steps of research: sampling, data collection, data analysis
• Cannot be minimized by increasing the size of the study

Selection bias

Definition
• Systematic error that arise from the procedure used to select subjects or from factors that influence participation
  – A selection bias is present when the association between the exposure and the outcome differs between participants and non participants
Sources of selection bias

Participation bias (self-selection)

- Participants who volunteer can be different than those who don’t volunteer
  - ex: more health-conscious, sicker
- The association between the exposure and the outcome is different for those who participated in the study compared with those who are in the target population

Sources of selection bias

Losses to follow-up

- In a longitudinal follow-up, drop-outs can raise a bias if the drop-out rate is different between the two study groups and if drop-outs are related to the study outcome
- The association between the exposure and the outcome is different between subjects who completed and who did not completed the study
- Example:
  - Drop-out rates among users of a new medication is higher than those among standard treatment users because of adverse events

Sources of selection bias

Other sources of selection bias

- Healthy worker effect
- Berkson’s Bias
- Detection bias
- Screening bias

See selected useful references
Information bias

Definition
• Systematic error that arises when information collected about study subjects is erroneous
• Synonym : Misclassification
• Misclassification of exposure or outcomes of the study subjects
• Various types of information bias

Sources of information bias

Recall bias
• When the evaluation of exposures or outcomes is affected by the respondent’s memory
• Examples:
  – Patients can have difficulty to remember the exact name or dosage of their medications
  – They can have difficulty to remember details if health events appeared a long time ago

Desirability bias
• When the evaluation of exposures or outcomes is affected by the tendency of respondents to answer questions in a manner that will be viewed favorably by others
• Examples:
  – Underreporting of socially undesirable behaviors
    • Alcohol drinking, illicit drugs use, etc.
  – Overreporting of socially desirable behaviors
    • Exercise, adherence to medication, prescribing practices of physicians, etc.
Sources of information bias

Measurement scales validity
- The evaluation of exposures or outcomes can be affected by the validity of measurement scales/tools/questionnaires
- Important to use recognized, reliable and valid scales for the measure of self-reported data
- Examples:
  - Complex variables such as quality of life or severity of depression must be measured by reliable and valid tools, i.e. SF-12, Beck Depression Inventory (BDI)

Validity of diagnostic codes in administrative databases
- When using administrative databases for pharmacoepidemiologic research, the evaluation of exposures or outcomes can be affected by the validity of diagnostic codes
- These databases raise validity concerns because they are not created for research purposes
- Examples:
  - International Classification of Diseases codes (ICD-9 or ICD-10) for congenital malformations
  - Does the presence of a diagnostic code necessarily mean the presence of a congenital malformation? Does the absence of a diagnostic code necessarily mean the absence of a congenital malformation?
Sources of information bias

Standardization of information
- To minimize information bias, information has to be collected in a standardized way
- Examples:
  - All subjects have to complete the exact same self-administered questionnaire
  - Data should preferably be collected by one data collector or a group of well-trained data-collectors
  - Exposures and outcomes have to be evaluated in the same way between exposed and non-exposed subjects or between cases and controls
  - Data collectors should be blinded to the study groups of subjects to avoid observer bias

Sources of information bias

Other sources of information bias
- Inaccuracies of medical charts
- Lead time bias

Information bias
- Information bias (misclassification) can be non-differential or differential

Selected useful references
Information bias

Non-differential misclassification
- The misclassification is the same between study groups
- Related to the quality of the measurement instrument or method
  - Misclassification of the exposure is not related to the outcome and misclassification of the outcome is not related to the exposure
- Generally leads the measure of association (ex: RR, OR, etc.) toward 1

Information bias

Differential misclassification
- The misclassification is different across study groups
  - Between exposed and unexposed
  - Between case and controls
- Examples:
  - In perinatal case-control studies recall of the mother about exposures and drug use during pregnancy is not the same among women who had poor vs good pregnancy outcomes
- Can lead to an underestimation or overestimation of the measure of association (ex: RR, OR, etc.)

Some pharmacoepi-specific bias

Length of drug free bias
- When measuring incidence of drug use in administrative databases, some researchers use different drug free periods (ex: 6-months, 12-months, 24-months, etc.)
- Be cautious regarding the length of the drug free period because it can affect incidence measures

(Gardarsdottir et al., 2006)
Some pharmacoepi-specific bias

**Depletion of susceptibles effect (prevalent user bias)**
- When studying drug adverse events and related health care services use in observational studies, patients who have already used a drug in the past can have less chances of adverse events associated with current use of the drug
  - Patients who remain on a drug can tolerate it
  - Patients who cannot tolerate the drug stop it and select themselves out of the population at risk
- Solution: Conduct new-users studies or consider past use of the drug as a potential risk modifier

(Moride & Abenhaim, 1994; Ray, 2003)

Some pharmacoepi-specific bias

**Many others...**
- Immortal time bias
- etc.

Confounding

**Definition**
- When the effect of the exposure is mixed together with the effect of another variable
- A central issue in observational study designs because of the absence of randomization
Confounding

Confounding variable
- Variable associated with the exposure and independently associated with the outcome

Exposure
Not equally distributed between exposed and unexposed subjects

Outcome
Can have an influence on the outcome

Confounding variable
Association we want to evaluate in the study

Confounding

In RCTs
- Because of random allocation of treatments, confounding factors are equally distributed between study groups

Exposure
Not equally distributed between exposed and unexposed subjects

Outcome
Can have an influence on the outcome

Confounding variable

Confounding

In observational studies – Confounding by indication
Example: Prospective cohort study of the effectiveness of different antidepressants for fibromyalgia

Patients suffering from fibromyalgia followed by a primary physician

Duloxetine users
Serotonin-Norepinephrine Reuptake Inhibitor
- Disease severity
- Adverse events susceptibility
- Treatments tried in the past
- Socioeconomic status
- Expectations
- etc.

Citalopram users
Selective Serotonin Reuptake Inhibitor

Effectiveness and safety outcomes
- Pain intensity
- Quality of life
- Sleep quality
- Depressive symptoms
- Adverse events
Confounding

- Control of confusion
  - Measurement of all potential confounding factors
  - Restriction
  - Matching
  - Stratification
  - Multivariate analysis
  - Propensity scores
  - ...new methods are increasingly being published

Validity of studies

- To be valid, pharmacoepidemiologic studies must have:
  1) Internal validity
     - Least possible bias
  2) External validity
     - Capacity to generalize the study findings

Generalizability

- Capacity to generalize the study findings to the target population
- External validity of a study
Generalizability

To evaluate the generalizability of a study

• Is the study population representative of the population in which you want to apply your findings?
• Were strict selection criteria applied?
• Does the study population have special characteristics that are different from the general population?

Example 1
Multicenter randomized double-blind placebo-controlled trial about safety and efficacy of varenicline for smoking cessation compared to bupropion or placebo

Inclusion criteria:

• 18 to 75 years of age
• smoked 10 or more cigarettes per day
• <3 months of smoking abstinence in the past year
• were motivated to stop smoking

Exclusion criteria:

• Any serious or unstable disease within 6 months; seizure risk
• clinically significant cardiovascular disease within 6 months; uncontrolled hypertension; severe chronic obstructive pulmonary disease
• history of clinically significant allergic reaction requiring treatment
• history of panic disorder, psychosis, bipolar disorder, or eating disorders; alcohol or drug abuse/dependency within the past year; use of tobacco products other than cigarettes; use of nicotine replacement therapy, clonidine, or nortriptyline within the month prior to enrolment; and body mass index less than 15 or greater than 38 or weight less than 45.5 kg
• prior exposure to bupropion; varenicline; pregnant women; women not practicing contraception
Generalizability

Example 2
External validity of epidemiologic and pharmacoepidemiologic studies conducted within the Régie de l’assurance maladie du Québec (RAMQ) administrative database

VALIDITY OF PERNATAL PHARMACOEPIDEMIOLOGIC STUDIES USING DATA FROM THE RAMQ ADMINISTRATIVE DATABASE

Example 2 (continued)
RAMQ administrative database → Quebec province insurance plan
• Covers all Quebec residents for the cost of physician visits, hospitalizations, and medical procedures
• Only covers a portion of them for the cost of prescribed medications
  – Individuals 65 years and older
  – Recipients of social assistance (welfare recipients)
  – Workers and their families who do not have access to a private drug insurance program
  – Approximately 43% of the overall Quebec population.

Over represents individuals of lower socioeconomic status

Capacity to generalize findings from studies conducted within the RAMQ prescription database can be affected by the particularities of the RAMQ medication insurance plan coverage

4. Data sources in pharmacoepidemiology
- Field studies
- Administrative databases
Data sources

Many possibilities...
• Field studies
• Administrative databases
• Patients registries
• Medical chart review
• Etc.

More than one approaches can be combined

Field studies

• Prospective recruitment of patients
  Ex:
  – Pharmacy-based cohort study
  – Hospital-based cohort or case-control studies

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ You collect and measure what you want</td>
<td>✓ Very costly (costs and time) as compared to the use of retrospective data because:</td>
</tr>
<tr>
<td>✓ Validity of exposure data</td>
<td>• Large samples is needed</td>
</tr>
<tr>
<td>✓ Validity of outcome data</td>
<td>• Recruitment can be long</td>
</tr>
<tr>
<td>✓ Control of confounding</td>
<td>• Long-term follow up is needed</td>
</tr>
</tbody>
</table>

✓ Not population based
✓ Losses to follow-up
✓ Representativeness issues (affected by selection criteria and willingness to participate)
Administrative databases

Some examples:
- Régie de l'Assurance Maladie du Québec (RAMQ) database, CAN
- Saskatchewan database, CAN
- Medicaid/Medicare, USA
- General Practice Research Database (GPRD), UK
- Other health insurance databases (private or public)

Strengths
- Large sample sizes
- Well defined study frames for drug utilization studies
- Lack of recall bias
- Possibility to analyse numerous exposures and outcomes at the same time
- Efficiency (more rapid and less expensive than field studies)
- Sometimes population-based

Weaknesses
- Not designed for research purposes
- Data on potential confounders is not always available
  - Sociodemographic risk factors
  - Lifestyle choices
  - Clinical variables
- Over-the-counter medication use
- Validity relies heavily on the validity of outcomes and diagnosis information
- Representativeness issues (population included in the database)

Can be completed by patient reported outcomes (Ex: Two-stage sampling)

Conclusion

- Pharmacoepidemiologic post-marketing studies provide important information about risks and benefits of drugs
- Methodologies and data sources are increasingly expanding in the field of pharmacoepidemiology
- This type of research should be valued by all stakeholders of drugs use
Questions

Thank you!