765 Pharmacoepidemiology - 3 credits

*PRE*-requisites: EPID 600 and BIOS 600 or equivalents

Instructor: Til Stürmer (a.k.a. Sturmer, Stuermer);

sturmer@unc.edu; Phone: 919 966 7433

January 13 – April 23, 2009

Meetings: Tuesday, Thursday, 2:00 – 3:15

Purpose: introduce students to most important issues and career options in pharmacoepidemiology; emphasize how non-experimental studies on drugs can draw from standard epidemiologic techniques and explore the ways in which drugs present unique research challenges and opportunities.

Structure: lectures, seminars, case studies, invited speakers

Grading:

30% class participation
40% term paper (small groups)
30% student evaluation and presentation of assigned papers

Each will be graded on a 4 point scale
- fully acceptable by professional colleague
- evidence of a colleague in training
- some merit but insufficient for scientific interchange
- unacceptable or incomplete

Honor code:

Each student is required, and therefore assumed, to be familiar with the Instrument of Student Governance and to abide by it. The Instrument is available at http://instrument.unc.edu/. Other information on the UNC Honor System is at http://honor.unc.edu/.

Appendix A to the Instrument states that each student is expected to “Sign a pledge on all graded academic work certifying that no unauthorized assistance has been received or given in the completion of the work.” It is the student’s responsibility to know this pledge, write it down, and sign it on all graded academic work, whether or not a designated space is provided for it on the assignment or exam. The instructors reserve the right to deduct points without advance warning for failure to comply with this requirement.

Basic definition of “unauthorized assistance” for the graded assignments consists of using any unreferenced materials or computer programs. If you have any specific questions about what constitutes “unauthorized assistance” while completing an assignment, please ask me.
Pharmacoepidemiology is a public health discipline that relies on non-experimental (epidemiologic) methods to assess wanted and unwanted drug effects to support decision-makers in the absence of specific evidence from experimental studies (randomized controlled trials). This course is for clinicians, pharmacists, epidemiologists and scientists from related fields in academia, industry and regulatory agencies. It will provide an introduction and overview of pharmacoepidemiologic methods, databases and review examples of current research. From case reports to cohort studies, the course will look at specific aspects and potential pitfalls of epidemiologic study designs when applied to the study of drug effects, including the use of administrative databases and novel methods to control for selection bias and confounding.
Selection of additional pharmacoepidemiology textbooks:


New book with much extended scope compared with prior versions (see below). Good examples. Quite expensive (PERM from now on).

Provides the reader with an overview of pharmacoepidemiology, as well as the epidemiology of specific disease states. Includes an annotated bibliography of pharmacoepidemiologic studies as of 10 years ago. A little old, currently on sale.

No textbook but comprehensive behind-the-scenes look at issues that affect everyone: our shortage of data comparing the worth of similar drugs for the same condition; alarming lapses in the detection of lethal side effects; the underuse of life-saving medications; lavish marketing campaigns that influence what doctors prescribe; and the resulting upward spiral of costs that places vital drugs beyond the reach of many Americans.

Selection of epidemiology textbooks (for the non-epidemiologists)

The bible in its 3rd edition. Still the best and cheaper than many others. A must have for anyone interested in non-experimental population research.

A simple (but neither simplistic nor outdated as so many others) overview of the concepts that are the underpinnings of epidemiology, so that a coherent picture of epidemiology thinking emerges. The emphasis is not on statistics, formulas, or computation, but on epidemiologic principles and concepts".

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Team term paper pharmacoepidemiology course Epid 765

The team term paper should provide an overview about a chosen drug-outcome association. This is not to imply that the field of pharmacoepidemiology is restricted to this kind of study, but rather that whereas other issues in pharmacoepidemiology are not unique to the field, many challenges when addressing drug-outcome associations using non-experimental methods are.

The overview should be based on the published literature and not cover a topic that has been recently reviewed (2005 or later).

The paper should develop the history of the evidence ideally from case-report (or any other form of signal) to the current state of knowledge. The paper should indicate an understanding of the advantages and disadvantages of specific studies based on their methodology, make a non-formal summary of the evidence taking these into account, discuss limitations of the existing evidence and whether and how these can be addressed, and finally propose possibilities to overcome evidence gaps based on existing or new data.

Each team should submit a very brief (1 paragraph, max. 250 words) proposal for a topic addressing why this topic was chosen and whether it is suited to address the above mentioned points. **These brief proposals are due 2/26.** I will either OK these topics or discuss problems/alternatives with each team in the week before the spring brake. **Each team will need an agreed upon topic before the spring break (by 3/5).** Each team will present their paper in class at the end of the course. We will have 20 minutes per team including discussion. The presentation will be limited to 12 minutes and 15 slides. **The term paper is due 4/16 at midnight.**

The term paper should conform to the instructions for authors of Pharmacoepidemiology and Drug Safety (review category). In addition, there should be at least one figure and not more than 3 tables. All facts presented should be referenced and any plagiarism avoided. Please do not consult with experts in the field (you can ask me questions). Some of these papers may lead to publications while others will not.

I will judge these papers according to the understanding of the difficulties to make decisions about the benefit to harm ratio of drugs in the presence of less than ideal data, limitations of the existing evidence, and the proposal to overcome these. The latter should be based on an understanding of real life constraints (rather than “we propose a RCT enrolling 100k people to be treated over 20 years”). General statements (“could be biased”) should be avoided. Instead, an assessment of the direction and magnitude of potential biases of a specific study in relation to other studies should be made (“did not control for SES. Low SES (defined as) vs. high SES (defined as) has been shown to be a risk factor for Y (RR;95%CI) and to be associated with barriers to receiving treatment A (OR;95%CI); thus not controlling for SES would tend to bias in the direction of C and the magnitude would be sufficient to explain the observed result/discrepancies”).
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Lesson 1: What is pharmacoepidemiology?

Readings:
Table of contents, Textbook of Pharmacoepidemiology
Table of contents, Pharmacoepidemiology and Therapeutic Risk Management
Kenneth J. Rothman, Foreword to PERM
Brian L. Strom, What is pharmacoepidemiology? Textbook chapter 1

Lesson 2: The contribution of PE to the study of drug uses and effects

Readings:
Abraham G. Hartzema, Hugh H. Tilson, K Arnold Chan. The contribution of PE to the study of drug uses and effects, and risk management. PERM chapter 1
Lesson 3: Role for epidemiology in drug development

Readings:

Robert F. Reynolds. Epidemiology in Drug Development. PERM chapter 2

Student presentation Lesson 3: The future of drug Safety

Executive summary of Institute of Medicine (IOM) report on “The future of Drug Safety: Promoting and Protecting the Health of the Public”

Lesson 4: Drug approval

Readings:


Silvio Garattini, Vittorio Bertele. The mandate of the European Medicines Evaluation Agency. PERM chapter 4

Student presentation Lesson 4: Rosiglitazone and myocardial infarction


Lesson 5: Special issues in PE I

- Confounding (by indication, frailty)
- Selection bias


Student presentation Lesson 5: Flu vaccine and mortality in the elderly


Additional readings:


Lesson 6: Special issues in PE II

- New user design


Student presentation Lesson 6: Comparative effectiveness of osteoporosis drugs

Lesson 7: Special issues in PE III

- Propensity scores

Readings:


Student presentation Lesson 7: Variable selection for PS models


Lesson 8: Academic detailing

Guest speaker: Frank May, M.App.Sci. (Pharm)

Readings:

Soumerai SB, Avorn J. Principles of educational outreach ('academic detailing') to improve clinical decision making. JAMA 1990;263:549-56.


No student presentation
Lesson 9: Special issues in PE III

- Propensity scores continued

Readings:


Student presentation Lesson 9: Aspirin and CRC


Lesson 10: Special issues in PE IV

- Non-uniform effects

Readings:


Student presentation Lesson 10: Subgroup analyses

Lesson 11: Doubly robust Estimation in PE (Michele Jonsson Funk)

No readings

**Student presentation Lesson 11**: Beta-blockers in patients with heart-failure


Lesson 12: Hormone Therapy and Myocardial Infarction

Readings:


Plus editorial, responses, and 2 rejoinders

**Student presentation Lesson 12 (ITT analyses only, no need to talk about adherence adjusted effects):**


Lesson 13: Instrumental Variables in PE

Guest speaker: M. Alan Brookhart, PhD

Readings (the second reading is optional):


**Student presentation Lesson 13:**

Lesson 14: Patient Reported Outcomes

Guest speaker: Cynthia J. Girman, PhD

Readings (not all required):


Student presentation Lesson 14:


Lesson 15: External Control for Confounding

Readings:


Student presentation Lesson 15:

Lesson 16: CRO Perspective of PE

Guest speaker: Axel Olsen

No readings

Student presentation lesson 16:


Lesson 17: Sources of Data for PE

Readings:

Syed R. Ahmad, Norman S. Marks, Roger A. Goetsch. Spontaneous reporting in the United States. Textbook chapter 7

Brian L. Strom. Overview of automated databases in pharmacoepidemiology. Textbook chapter 11

Andy Stergachis et al. Examples of automated databases. Textbook chapter 12

No student presentation (spring break)

Lesson 18: Relationships with industry in PE research

Guest speaker: Jerry Avorn, Harvard Medical School

Readings:


http://www.innovation.gov.uk/lambertagreements/
http://www.medpagetoday.com/MeetingCoverage/ACC/8972
Lesson 19: Current developments in PE

- Comparative effectiveness

Readings:

Brian L. Strom. The use of pharmacoepidemiology to study beneficial drug effects. Textbook chapter 21


Additional reading (not required):


Student presentation lesson 19:


Lesson 20: Industry perspective of PE

Guest speaker: Sara Ephross, PhD, GlaxoSmithKline

Readings:


Student presentation lesson 20:

Lesson 21: PE in Denmark

Guest speaker: Jesper Hallas, MD, PhD, University of Southern Denmark

Readings:


Student presentation lesson 21:


Lesson 22: Pharmacovigilance

Readings:

Ahmad SR, Oullet-Hellstrom RP, McCloskey CA. Pharmacovigilance. Chapter 5, Pharmacoepidemiology and Therapeutic Risk Management (Hartzema, tilson, Chan (Eds.)

Student presentation lesson 22:


Lesson 23: Immortal and Immeasurable Time

Readings:


Student presentation lesson 23:

Lesson 24: Student group project presentation I (groups 1 & 4)

Student presentation lesson 24:


Lesson 25: Student group project presentation II (groups 2, 3, 5)

Lesson 26: Ethics of placebo controls - academic perspective of PE

Guest speaker: Ken Rothman

Readings:


Rothman KJ, Michels KB, Baum M. Declaration of Helsinki should be strengthened. BMJ 2000;321:442-5.

Michels KB, Rothman KJ. Update on unethical use of placebos in randomized trials. Bioethics 2003;17:188-204.

Wolinsky H. The battle of Helsinki; two troublesome paragraphs in the Declaration of Helsinki are causing a furore over medical research ethics. European Molecular Biology Organization 2006;7:670-2.

http://www.socialmedicine.org/2008/06/01/ethics/fda-abandons-declaration-of-helsinki-for-international-clinical-trials/

Lesson 27: The need for comparator drugs

Guest speaker: Robert J Glynn, ScD, PhD

Readings:
Lesson 28: PE Bouillabaisse (readings by topic)

- Off-label drug use

- Inappropriate prescribing

- Science vs. regulation