SAPh 8610 (SAPh 5610/Phar 5610) Pharmacoepidemiology

Course Syllabus Fall 2019
3 Credits

This course adheres to the items listed in the College of Pharmacy Central Syllabus:
https://docs.google.com/a/umn.edu/document/d/1artQ5e1rbzxe8lEtWo7BE8k8snZAEgMMz_QcW8yJ-II/edit?pli=1

Meeting Times & Locations

Day	Time	Duluth Room	Twin Cities Room
Monday	3:30 – 5:30pm	LSci 205A	WDH-7-173

Course Website: http://canvas.umn.edu

Instructional Team

If you need assistance with the course, contact one of the Teaching Assistants.

Technology Help, Duluth: 218-726-8847 itsshelp@d.umn.edu
Technology Help, Twin Cities: 612-301-4357 help@umn.edu

Faculty Office Hours: by appointment

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Course Description

Course content: Pharmacoepidemiology is the study of the uses and effects of drugs in patient populations. The science of pharmacoepidemiology borrows from pharmacology and epidemiology. This course will introduce students to the field of pharmacoepidemiology including study methodology, relevant statistics, data sources, measurement of treatments and outcomes, sources of bias and control of confounding, techniques to reduce bias and confounding, survival analysis and regression techniques, interpretation of results, and drug safety surveillance and risk management.

Course format: This course is mainly lecture-based. Students are expected to prepare for each class, as debate and discussion of various concepts presented in class will take place. Near the end of the course, students will be expected to use information gained throughout the course to compose a written critique of a pharmacoepidemiology study and then orally present their critique in class.

Prerequisites

- SAPh, ECP or SPH Graduate student or 2nd, 3rd or 4th year pharmacy student. First year students may enroll with permission of course directors. First year students will need to show that they have had previous relevant courses in epidemiology, or public health.

Requirements

Course Materials

Required

- Textbook of Pharmacoepidemiology, 2nd Edition 2013. Editors: Strom BL, Kimmel SE, Hennessy S. ISBN: 978-1-118-34486-6 (Available from Biomed Library)
- Essentials of Clinical Research. 2014, Editor: Stephen Glasser. ISBN: 978-3-319-05470-4 (Available online from Biomed Library). http://primo.lib.umn.edu/TWINCITIES:mncat_discovery:TN_scopus2-s2.0-84961373238
- Causal Inference. Hernán MA, Robins JM (2017). Boca Raton: Chapman & Hall/CRC, forthcoming. Available online at: http://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

Optional (for additional perspective)

- Modern Epidemiology; 3rd Edition. Eds. Rothman KJ, Greenland S, Lash TL. Lippincott Williams & Wilkins, Philadelphia, 2008. (Available online from Biomed Library)
- Epidemiology, Fifth edition (Available online from Biomed Library)
- Medical Epidemiology 2005 (Available online from Biomed Library)

Computer / Technology Requirements

- The University of Minnesota computer requirements are listed here: http://www1.umn.edu/moodle/start/technical.html

Attendance Policy

Students are expected to attend every class for which they are registered. Students are expected to attend classes on the campus where they are enrolled. Instructors may choose to take attendance. When a student is unable to attend a class for health or family reasons, the instructor must be informed in advance.

Goals & Objectives

Course Goals

Main course concepts:

The aim of the course is to help students acquire a basic understanding of the concepts and practice of pharmacoepidemiology.

Learning Objectives

1. **Discuss** the concept of pharmacoepidemiology
2. **Compare and contrast** typical pharmacoepidemiologic study designs and explain their strengths and weaknesses
3. **Discuss** the roles that pharmacoepidemiology studies have had in the past regarding drug use and health outcomes and the future roles that pharmacoepidemiology can play in drug safety surveillance and comparative drug effectiveness and safety
4. **Debate** the threats to validity that are possible in pharmacoepidemiology studies and the variety of solutions available to avert or control for these threats
5. **Understand** the use of regression and matching techniques used in pharmacoepidemiologic research
6. Using the information provided by the text, lectures, and assigned readings, **compose** a written critique of a recently-published pharmacoepidemiology study and **orally present** this critique in class

Assessments and Grading

Assignments and learning activities

Graded Assessments

- Class participation/attendance (20%)
- Midterm exam – multiple choice, short answer/essay (40%)
- End-of-semester written critique of journal article (20%)
- End-of-semester oral presentation of journal article (same as above) [slides, 15-20 minutes] (20%)

The midterm exam, written critique, presentation and class participation/attendance will be graded by the course directors.

Thorough reading of assigned readings prior to class, attendance and class participation is expected. The student will take the midterm exam, select one study from recently-published pharmacoepidemiology studies, compose a written critique of the study and orally present this critique in class. You will be expected to have prepared for each class and completed any homework assignments prior to class. Class participation points will be assigned based on course director's assessment of your preparedness for class which will be assessed through your class participation.

Course Letter Grades

Grade	A	A-	B+	B	B-	C+	C	C-	D	F
%	>93	90-92	87-89	83-86	80-82	77-79	73-76	70-72	60-69	<60

Late paper or presentation material submission

Late papers or late presentation materials will be assessed a penalty. Your grade will be reduced by 5% for each day that your materials are late.

Re-grade Policy:

There will be no re-grades in this class**.**

Minimum Passing Level: C-

Schedule

<table>
<tr><th colspan="2">Week 1</th></tr>
<tr><td>Monday
Sept 9</td><td>

What is Pharmacoepidemiology? Wendy St. Peter

- Distinction between pharmacoepidemiology, epidemiology, and clinical pharmacology
- Historical Background
- Potential Contributions

Required Reading

Textbook of Pharmacoepidemiology

- Chapter 1 (pages 3-16)
- Chapter 4 (pages 40-41)

Optional Readings:

- Wettermark B. The intriguing future of pharmacoepidemiology. *Eur J Clin Pharmacol*. 2013; 69 (Suppl 1):S43–S51.

Basic Principles of Statistics and Application to Pharmacoepidemiology studies Wendy St. Peter

- Causality, associations and strength of evidence
- Hypothesis testing

Required Reading (note: find a reading below that you can understand for each topic above)

Textbook of Pharmacoepidemiology

- Chapter 2 (pages 17-18, 20-21-Causality, associations, strength of evidence)
- Chapter 3 (pages 30-33, Sample size, Type 1 and 2 errors, power)
- Chapter 5 (pages 57-58, Hypothesis testing)

Essentials of Clinical Research (ECR)

- Chapter 16 (pages 357-359-Causality)
- Chapter 2 (pages 11-21, Hypothesis testing, Type 1 and 2 errors, strength of evidence)
- Chapter 15 (pages 327-344; Hypothesis testing, statistical power, sample size, Type 1 and 2 errors
- Chapter 18: pages 373-383, Hypothesis testing,

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<tr><th colspan="2">Week 2</th></tr>
<tr><td>Monday
Sept 16</td><td>

Pharmacoepidemiologic Study Designs
Wendy St. Peter

- Basic features, strengths and weaknesses of pharmacoepidemiology study designs
  - Case reports and case series
  - Ecological studies
  - Cross-sectional studies
  - Case-control studies
  - Nested-case control studies

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	○ Cohort studies **Homework** 1) Describe basic differences between cross-sectional study, case-control study and cohort study, with 1 strength and 1 weakness for each of these 3 study designs. 2) Which of the study designs above, if any, could be used to determine the causal association between a drug and an outcome (such as mortality)? **Required Reading:** **Pharmacoepidemiology Text** • Chapter 2 (pages 22-29) **Essentials of Clinical Research (ECR)** • Chapter 2 (pages 21--Strength of Relationships to page 31) **Other Required Readings** • Etminan M & Samii A. Pharmacoepidemiology I: A review of pharmacoepidemologic study designs. Pharmacotherapy 2004;24:964. *Read pages 964-966 (don't read section on case-crossover studies) and 968 (confounding bias only).* • Etminan M. Pharmacoepidemiology II: the nested case-control study-a novel approach in pharmacoepidemiologic research. Pharmacotherapy 2004;1105-1109. **Bring a hardcopy to class or be able to access electronically in class for an exercise** • Johnsen SP. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib and other NSAIDs. Arch Intern Med 2005;165;978-984. • Block GA. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. Kidney International 2010;78:578-89.
Week 3	
Monday Sept 23	**Sources of Data and Data Extraction** **Cathy Starner and Pat Gleason** • Administrative datasets (Medicare, commercial) • Medical records (Structured data, Unstructured Data) • Critical assessment of data sources • Limitation of data sources **Required Reading: Pharmacoepidemiology Text** • Chapter 8 (Pages 118-122) • Chapter 9 (pages 123-143 & 152-177) with a focus on the strengths and weaknesses sections. **Measurement of treatments and outcomes** **Cathy Starner and Pat Gleason** • Baseline disease status

	• Drug effectiveness versus efficacy
	  ○ Treatment effect heterogeneity
	• Drug exposure
	  ○ Intent-to-treat versus as-treated
	  ○ First fill, days' supply, adherence, persistence
	• Outcomes
	  ○ Clinical outcomes
	  ○ Economic outcomes
	
	Required Reading: Textbook of Pharmacoepidemiology
	• Chapter 6 (Pages 65-67)
	• Chapter 20 (Pages 314-322)
	• PQA Adherence Measure Specifications on Proportion of Days Covered (PDC) (see class folder)
	• PDC Measure Calculation (see class folder)
	
	Homework: Use pharmacy claims data extract for sample members (see 'Sample members for PDC calculation' excel spreadsheet in class folder) to calculate adherence using proportions of days covered (PDC) calculation for statins for members 1 and 5. Feel free to try calculations for other members as well for extra practice.

Week 4	

Monday Sept 30	**Bias, Confounding and Control of confounding, Validity**
	Holly Epperly Budlong
	• Validity
	  ○ Face validity
	  ○ Internal validity
	  ○ External validity
	• Types of bias
	  ○ Selection bias
	  ○ Indication bias
	  ○ Measurement bias
	  ○ Information bias
	  ○ Misclassification (disease or exposure)
	  ○ Immortality bias
	  ○ Lead time bias
	
	Homework: Choose 1 type of bias described in the required reading (Delgado-Rodriguez article) that is most interesting to you and use available class or online resources to further describe the type of bias and implications to study results.
	
	Write up your answer to the homework and please email your answer to Dr. Budlong by 12 midnight on Saturday September 28th.
	
	Required Reading:
	Delgado-Rodrıguez M and Llorca J. Bias. J Epidemiol Community Health 2004;58:635–641.
	
	Essentials of Clinical Research. Chapter 17: Bias, Confounding, and Effect Modification (Interaction): pages 363-372.

Week 5	

Monday
Oct 7
	Introduction to Statistics, and Regression Techniques used in Pharmacoepidemiology
	Eric Weinhandl
	
	• Statistical power and sample size, Type 1 and 2 errors, p-values
	• : Means (SD), medians (25_{th}-75_{th} percentiles) and standardized differences
	  o Example: Assessing patient characteristic tables
	• Regression Modeling Techniques
	  o Logistic regression
	  o Linear regression
	  o Gamma regression (briefly introduce)
	  o Poisson regression (briefly introduce)
	  o Cox regression (briefly introduce)
	
	• Difference between OR and RR and calculations for OR and RR
	• What is HR and how it is different than RR
	• What is the difference between relative risk, risk ratio, and rate ratio
	• Interpretation of results (RR, HR, absolute risk reduction, numbers needed to treat)
	Required reading: TBA
	Homework: TBA

Week 6	
Monday Oct 14	**Analytic Approaches for Improved Confounding Control** **Eric Weinhandl** • Difference in difference approach for confounding control • Propensity scores • Instrumental variables (brief introduction) **Homework:** Read required readings below and answer the following questions 1. What types of variables should and should not be included in propensity score models? 2. Explain why p-values should not be used to diagnose the quality of matching, and describe what methodology should instead be used. 3. What is the definition of an instrumental variable? (That is, what are the conditions that define an instrumental variable?) **Required Reading:** • Glynn RJ et al. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic and Clinical Pharmacology and Toxicology 2006;98;253-259 • Persson F et al. Dapagliflozin compared to DPP-4 inhibitors is associated with lower risk for CV events and all-cause mortality in type 2 DM patients (CVD-REAL Nordic): a multinational observational study. (in press) and Appendices S1 and S2. • Ertrefaie A. A tutorial on the use of instrumental variables in pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2017;26(4)357-367.

Week 7	
Monday Oct 21	**Selected Pharmacoepidemiology Applications: Drug Utilization, Comparative Effectiveness and New User Design** **Wendy St. Peter** ○ Review expectations for article review and presentation (course directors) ○ Drug utilization studies ○ Comparative effectiveness and safety research (observational studies) ○ Active comparator new user design **Homework TBD:** 1. Review the 'Pharmacoepidemiology Article Review and Presentation Evaluation Form' and come to class with questions for course directors 2. Read Coding Systems by Optum, RxNorm Overview, Generic Product Identifier Q1: Why are hierarchical numerical coding systems used to categorize drugs within databases? Q2: What are the similarities and differences between NDC, GPI and RXNorm drug coding? 3. Read article: Lund JL et al. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep 2015;2(4):221-228. Q1: In what direction does confounding by indication bias (selection bias) change the effect estimate? (i.e. exaggerate positive drug effects or exaggerate safety effects?) Q2: How does an active comparator new user design reduce selection bias? Q3: In which direction does 'healthy initiator effect' or 'healthy user effect' change the effect estimate? (i.e. exaggerate positive drug effects or exaggerate safety effects?) Q4: How does an active comparator new user design reduce healthy user (initiator) effect? **Bring or have access to these articles for in-class use (see class folder)** a. Yusuf AA. Utilization and costs of medications associated with CKD-MBD enrolled in Medicare Part D. AJKD 2014. b. Yusuf AA. CE of calcium acetate and sevelamer on clinical outcomes in elderly HD patients enrolled in Medicare Part D. AJKD 2014.

Week 8	

Monday Oct 28	**Selected Pharmacoepidemiology Applications: Drug Safety Surveillance and Risk Management and Pharmacovigilance**
	Holly Epperly Budlong
	• Drug Safety
	  ○ Drug-drug interactions
	  ○ Adverse drug events
	  ○ Classification criteria
	  ○ Errors of omission
	  ○ Errors of commission
	• Signal sources and generation
	• Signal identification
	• Signal detection algorithms
	• Dis-proportionality Analysis
	
	Homework: After reading required reading, please answer the following question:
	
	• In your own words and based on your own experience, explain reasons why drug safety surveillance and risk management and pharmcovigilance are important?
	
	Write up your answer to the homework and please email your answer to Dr. Budlong by 12 midnight on Saturday October 26th.
	
	Required Reading: Textbook of Pharmacoepidemiology
	• Chapter 22 (pages 370-378, 384-392)

Week 9	
Monday Nov 4	**Midterm Exam:**
Week10	
Monday Nov 11	**Principles of Survival Analysis and other Regression Techniques** **Rui Zhang**\ 4. Censoring 5. Hazard function; survival function 6. Kaplan-Meier and log rank test 7. Cox Proportional Hazard regression and hazard ratios **Homework:** Read the Kadra A article and VassarStats tutorial (below) and answer the questions. Q1: Why do we need Kaplan-Meier estimate? Q2: Use the tool from the VassarStats website to calculate the example in Figure 1 in the Kalra A. article. **Required Reading:** 8. Kalra A. The basics of Kaplan–Meier estimate. J Pract Cardiovasc Sci 2016;2:187-9, 9. Tutorial_Kaplan-Meier Survival Probability. http://vassarstats.net/survival.html or PDF on course website.

	10. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. Br J Cancer. 2003 Jul 21;89(2):232-8 **11.** Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. Br J Cancer. 2003 Aug 4;89(3):431-6
Week 11	
Monday Nov 18	**Selected Pharmacoepidemiology Applications—Systematic Review and Meta-analysis** **Arun Kumar** **Homework:** TBD
Week 12	
Monday Nov 25	**Miscellaneous topics** **Eric Weinhandl and Wendy St. Peter** Topics may include some or all of the following 12. Sensitivity analyses 13. Update on FDA a. Patient preferences b. Patient-reported outcomes c. Using claims data analyses to imitate clinical trials **Homework TBD:** 1) Using required reading and other information learned in class, critique patient characteristic tables from Yusuf A. Comparative Effectiveness…Am J Kidney Dis 2014;64:95-103, Block GA. Cinacalcet hydrochloride..Kidney Int 2010;78:578-589, and Arnold ME. Impact of pharmacist intervention…Am J Health-Syst Pharm 2015;72(suppl 1);S36-42. a. Should p-values be used to compare intervention and control groups? b. When should mean +/- SD be used, when should median and IQR (25th-75th percentile) be used to represent central patient characteristics? c. Explain value of using standardized differences to evaluate differences in patient characteristics. 2) Using required reading, describe the advantage of using a "new user" study design over analysis of current or existing phosphate binder users in the article Yusuf A. Am J Kidney Dis 2014;64:95-103. 3) Explain how difference-in-difference analyses resolve the problem inherent in before-after studies using Chertow GM. Epoetin alfa and outcomes in dialysis amid regulatory reform. JASN 2016;27. Required Reading: • Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Communications in Statistics-Simulation and Computation, 2009;38:1228-34. • Textbook of Pharmacoepidemiology ○ Page 325: New Users • Difference-in-difference estimation. https://www.mailman.columbia.edu/research/population-health-methods/difference-difference-estimation

Week 13	
Monday Dec 2	**Oral Presentations**
Week 14	
Monday Dec 9	**Oral Presentations and Course Evaluation**