EPID 765

Methods and Issues in Pharmacoepidemiology

Spring 2019

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EPID 765 Pharmacoepidemiology

Lead-Instructor: Til Stürmer, MD, PhD
Co-Instructor: Michele Jonsson Funk, PhD

- January 10 – April 25, 2019
- Tuesday, Thursday, 2:00 – 3:15
- Room: MGG - 2301

- Materials: UNC Sakai; EPID765.001.SP19

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EPID 765 Course Objectives

- Important issues and career options in PE
- Challenges and opportunities of non-experimental studies of drug effects
- Tools necessary to design and evaluate PE studies (conduct requires addtl. skills)

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EPID 765 Structure

- First half (before spring break)
  - Methodological topics
    - 25' unstructured discussion
    - 30' lecture (slides)
    - 20' journal club (student led)
- Second half (after spring break)
  - TBD guest topics (guest speakers)
    - 55' lecture (slides)
    - 20' journal club (student led)

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EPID 765 Readigns and Expectations

- Readings
  - Required
    - 1 topic specific paper
    - 1 journal club article
  - Suggested
    - Additional topic specific papers for later/reference
- Expectations
  - Required readings
  - Active class participation
  - Lead one journal club
  - Term paper

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EPID 765 Journal Club

- During the last 20 minutes of class
- Provide a brief summary of the paper (3 minutes, absolutely not more than 5!)
- Lead the discussion covering
  - Important aspects of methods, results, and conclusions
  - Do not try to cover everything, but rather focus on specific aspects
  - Are the conclusions supported by the data presented?
  - Would you change clinical practice based on the data presented?

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EPID 765 Term Paper

- Provide succinct (<3,000 words) overview of a drug effect on an outcome
  - Summarize the existing evidence
  - Discuss methodological limitations of studies
  - Propose realistic study to address gap(s)
- Topic not recently reviewed (>=2014)
- Up to 4 students can team up (self-eval)
- Brief proposals (250 words) due 2/27
- Class presentation 3/26 or 3/28
- Final paper due 4/8

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EPID 765 Pharmacoepidemiology

- Grading
  - 30%: Class participation
  - 30%: Discussion lead
  - 40%: Term paper
  - 4 point scale:
    - 4: fully acceptable by professional colleague
    - 3: evidence of a colleague in training
    - 2: some merit but insufficient for scientific interchange
    - 1: unacceptable or incomplete
  - Pass: 2.5
  - Honor: 3.5

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EPID 765 Inclusion & Diversity

- The SPH is a diverse, inclusive, civil and welcoming community
- Diversity and inclusion are assets that contribute to our strength, excellence and individual and institutional success
- We measure diversity and inclusion not only in numbers, but also by the extent to which students, alumni, faculty and staff members perceive the School's environment as welcoming, valuing all individuals and supporting their development
- We practice these commitments in the following ways:
  - Develop classroom participation approaches that acknowledge the diversity of ways of contributing in the classroom and foster participation and engagement of *all* students
  - Structure assessment approaches that acknowledge different methods for acquiring knowledge and demonstrating proficiency
  - Encourage and solicit feedback from students to continually improve inclusive practices

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EPID 765

Lesson 1:

What is Pharmacoepidemiology?

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Definitions of PE

- Application of
- epidemiologic reasoning, methods, and knowledge to the study of the
- uses and effects (beneficial and adverse)
- of drugs (and biologics), vaccines, and devices
- in human populations

Hartzema, Tilson, Chan: Pharmacoepidemiology and Therapeutic Risk Management 2008
In orange: new since 1991 2nd ed.

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Definitions of PE

- Study of the
- use of and the
- effects of
- drugs
- in large number of people

Strom, Kimmel: Textbook of Pharmacoepidemiology 2006

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Definitions of PE

- Study of
- distribution and
- determinants of
- drug-related events in
- populations and
- application of this study to
- efficacious drug treatment

Last: A Dictionary of Epidemiology. Oxford University Press. New York 1988

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Pharmacoepidemiology

- Pharmacon [greek]
  - Biologically active substance (includes drugs)
- Epidemiology
  - Study of the distribution and determinants of disease frequency in man

  MacMahon & Pugh, 1970
- Roots
  - Social pharmacology (Venulet 1974)
  - Elucidation and quantification of adverse effects (Leufkens 2001)

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Related Fields

- Pharmacology
  - Effects of drugs (including in vivo)
- Clinical pharmacology (MD) and clinical pharmacy (PharmD)
  - Optimize drug therapy in specific patient
  - Requires knowledge
    - Effects of drugs (beneficial and harmful)
    - Modification of effects by clinical status/comed
  - Important considerations
    - Kidney/liver function
    - Drug-drug/drug-gene interactions

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Clinical Pharmacology/Pharmacy

- Pharmacokinetics
  - What the body does to the drug
  - Timecourse of blood levels
    - Absorption
    - Distribution
    - Metabolism
    - Excretion
- Pharmacodynamics
  - What the drug does to the body
  - Relation between blood level and effect
- Causality assessment of adverse drug reactions (ADRs) in individuals

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Examples of PE

- Drug utilization research
- Drug effects
  - Unintended
  - Intended
- Analytic methods
- Practice guidelines
- Quality of care
- Drug development
- Regulatory affairs
- Therapeutic risk management

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Drug Utilization Research (DUR)

- Patients with hypertension
  - % treated?
  - % treated according to guideline?
- Potentially inappropriate prescribing
- Determinants
  - Regional
  - Insurance plan
  - Prescribing physician
  - Age, Sex
  - Race
  - SES

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Numbers (n) and age-standardized prevalences (%) of antihypertensive agents used as monotherapy in hypertensives of the MONICA Augsburg population. Men, age 25-64 years.

	1985		1990		1995		
	N	%	N	%	N	%	p-trend
Actual hypertensives	808	100.0	779	100.0	803	100.0	
Treated hypertensives	135	17.6	196	26.8	197	25.5	<0.001
Monotherapy	54	7.0	105	14.1	103	13.3	<0.001
Diuretics	7	0.9	15	2.1	4	0.5	n.s.
Betablockers	28	3.5	45	5.8	57	7.3	<0.01
Calcium blockers	18	2.4	36	5.0	29	3.7	n.s.
ACE-inhibitors	0	0	6	0.8	8	1.0	<0.05
Combination therapy	81	10.7	92	12.9	95	12.4	n.s.
Diuretic based	72	9.5	68	9.6	70	9.2	n.s.
+ Betablocker	40	5.2	38	5.3	26	3.4	n.s.
+ CCB and/or ACE	14	1.9	37	5.3	61	8.0	<0.001
Non-diuretic based	9	1.6	24	3.3	25	3.2	0.054

Gasse C, et al. Assessing hypertension management in the community: trends of prevalence, detection, treatment, and control of hypertension in the MONICA Project, Augsburg 1984-1995. J Hum Hypertens 2001;15:27-36.

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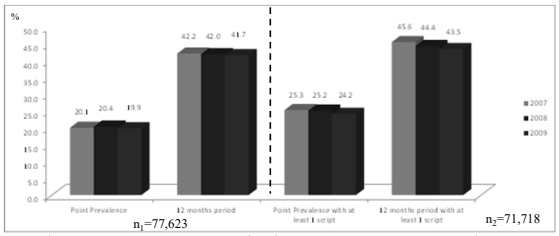
Prevalence of PIM among US Medicare Population



Total enrolled in Medicare previous 12 months

Total enrolled in Medicare with at least 1 script previous 12 months

Jiron M, Pate V, Jonsson Funk M, Sturmer T. Prevalence of potentially inappropriate medication prescribing among older US Adults. Pharmacoepidemiology and Drug Safety 2012, Volume 21(Suppl. 3), S30

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Point Prevalence of PIM by characteristics

Characteristic	Total	Total	Total
Year	2007	2008	2009
Sample size	5,183 (20.1%)	5,318 (20.4%)	4,987 (19.9%)
Sex			
Male	18.15	18.60	18.08
Female	21.14	21.40	20.91
Age, y (mean ± SD)	77.9 ±7.9	77.7 ± 8.0	77.7 ± 8.0
65-69	17.85	18.55	19.04
70-74	20.96	21.29	20.90
75-79	20.55	19.96	19.67
80-84	18.83	19.11	19.16
≥85	21.81	21.08	21.23
Race			
White	20.18	20.51	19.85
Black	22.17	22.36	23.05
Hispanic	17.97	17.97	19.58
Asian	17.06	16.92	15.51
Other	12.34	13.27	13.75
NA Native	14.79	17.67	17.39
Unknown	18.77	32.33	25.97

Characteristic	Total	Total	Total
Year	2007	2008	2009
Region			
South	21.45	21.76	21.06
Midwest	20.57	20.98	20.41
Northeast	17.03	17.45	17.34
West	17.21	17.26	17.19
US Territories	16.53	16.04	9.76
No. of drugs	5.7 ± 3.5	5.7 ± 3.7	5.7 ±3.7
1-2	11.29	11.86	11.55
3-4	21.69	21.12	20.23
5-9	36.95	36.33	35.33
≥ 10	58.81	58.69	56.08
Polypharmacy (≥5 drugs)			
Yes	40.42	40.17	38.95
No	16.12	16.09	15.45
Emergency visits 12 mo			
Yes	31.30	31.11	30.55
No	16.95	17.42	16.77
Hospitalization 12 mo			
Yes	28.81	28.72	28.60
No	17.71	18.31	17.74

Jiron M, Pate V, Jonsson Funk M, Sturmer T. Prevalence of potentially inappropriate medication prescribing among older US Adults. Pharmacoepidemiology and Drug Safety 2012, Volume 21(Suppl. 3), S30

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Drug Effects

- Randomized controlled trial (RCT)
- Scientific paradigm (experiment)
- Flip of coin leads to exchangeability at baseline (in expectation!)
- Blinding reduces potential for bias
- Differences in outcomes caused by/due to treatment
- Proves efficacy
- Prerequisite for drug approval

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RCT

- "Equipoise" needed for ethical reason
  - Non-utilitarian principle!
  - Physicians bound by Declaration of Helsinki
- Efficacy possible but not yet proven
- Window of opportunity
  - Some, but not too much evidence
  - Closed after approval vs. placebo (not: CER!)
    - primary indication
    - intended effect
  - May still be open for
    - Secondary indications
    - Unintended beneficial effects

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5 **S**hortcomings of RCTs

- Too **S**mall
  - to detect rare outcomes
- Too **S**imple
  - to detect interactions
- Too **S**elected
  - to be generalizable to all users and all indications
- Too **S**pecific
  - to assess all relevant outcomes
- Too **S**hort
  - to detect long-term effects

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Detection of ADR: Rule of 3

- Upper limit of 95% CI for incidence = 0 if no event occurred in N persons
- UL 95% CI = 3/N

Examples	N	Upper limit 95% CI
	10	30% (3/10 = 0.3)!
	30	10%
	100	3%
	300	1%
	1,000	0.3%
	10,000	0.03%

Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983;249:1743-5.

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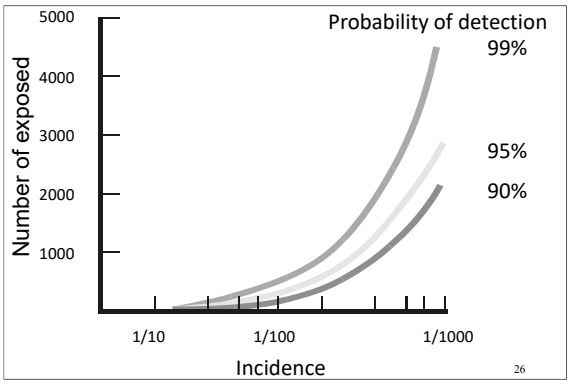
Too Small



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Examples for Incidence of ADR

Drug	Event	Incidence
Chinidine	Syncopy	1 / 100
Clozapine	Agranulozytosis	1 / 1,250
Enalapril	Angioedema	1 / 3,000
Lovastatin	Rhabdomyolysis	1 / 3,000
Dextrane	Anapylactoide reaction	1 / 4,000
Clopidogrel	Agranulozytosis	1 / 5,000
Halothane	Liver cell necrosis	1 / 30,000
Choramphenicole	Aplastic anemia	1 / 40,000
Cyclosporine A	Malignancy	?

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Too Short

- Usually weeks or month (rarely: years)
- Examples of exceptions:
  - Physicians' Health Study (PHS)
    - 325mg aspirin every other day 5* yrs
    - 50mg beta-carotene every other day 10 yrs
  - Women's Health Study (WHS)
    - 100mg aspirin every 2nd day 10 yrs
    - 600 IU vitamin E every other day 10 yrs
    - 50mg beta-carotene every other day 2* yrs
  - Women's Health Initiative (WHI)
    - 0.625mg estrogen, 2.5mg progesterone daily 5* yrs
    - 0,625mg estrogen daily 7* yrs

* trial arm stopped

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Nonexperimental Studies of Drug Effects

- Can be
  - Large enough to study rare outcomes
  - Include people with co-morbidity
  - Include people with co-medication
  - Include elderly, children, pregnant women
  - Include wider indication (e.g., less severe disease), off-label use
  - Variety of clinically relevant outcomes
  - Lagged and long term effects
- Not restricted by 5 S of RCTs

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Drug Effects

- Nonexperimental studies
  - No treatment assignment (experiment)
  - ASSUMPTION of exchangeability given measured covariates (epidemiology)
- Effectiveness vs. efficacy (RCT)
  - Real world vs. experiment
  - Effectiveness generally less pronounced (but: not necessarily so!)
  - Large, simple trials
  - Often comparative effectiveness

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Intended Drug Effects

- Strong potential for confounding by indication
  - Olli S. Miettinen. The need for randomization in the study of intended drug effects. Stat Med 1983;2:267-71.
  - Salim Yusuf, Rory Collins, Richard Peto. Why do we need some large, simple randomized trials? Stat Med 1984;3:409-20.
  - Sackett (EBM): "… disregard at once all articles on therapy that are not [RCTs]"
- Less potential with active comparator (CER)
  - E.g., Rosiglitazone vs. Pioglitazone and CVD
  - E.g., various bisphosphonates and fractures
  - E.g., antihypertensive classes and CVD
  - Conditioning on indication important!

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Unintended Drug Effects

- Not indication for treatment
  - Less confounded? (but: large overlap of RF for many outcomes)
- Automated
  - Spontaneous reporting systems
  - Large linked healthcare databases
    - FDA sentinel initiative
- Ad hoc, e.g.,
  - Coxibs and CVD
  - Insulin glargine/pioglitazone and CA
  - ARBs and cancer

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Analytic Methods

Above and beyond standard epidemiology:

- Availability of gold-standard (RCT)
- Detailed longitudinal electronic record on most prescription drug exposures over time
- Clear timelines
  - E.g., antidiabetic versus obesity
- Complex decisions about treatment
  - Patient (disease severity, frailty)
  - Healthcare providers (physician, pharmacist, etc.)
  - Health care system; society

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Practice Guidelines

- Evaluation of evidence
  - Possible biases (internal validity)
  - Magnitude (effect measures, CI)
  - Populations (external validity)
- Effectiveness over efficacy
- Comparative effectiveness
- Benefit-harm evaluation (scale?)
- Patient preferences
- Costs (pharmacoeconomics)

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Quality of Care

- Compare treatments with guidelines
  - E.g., Beers, START/STOPP, aspirin & statin & ACE & beta-blocker after MI
  - Keep in mind: population estimate useful despite individual contra-indications!
- Monitor drug use
  - Within hospitals, e.g., by department
  - By physician
  - Inform and discuss – do not police!
- Academic detailing

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Drug Development

- Prevalence of disease
  - Market (blockbuster vs. orphan)
- Incidence of disease
- Disease risk prediction
- Disease risk stratification
  - Identify high risk individuals for RCTs
- "You have to know the disease to study the drug"

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Regulatory Affairs

- Post marketing surveillance
  - Spontaneous reporting
  - Pharmacovigilance
  - Drug / disease registries
- Abuse / addiction
- Increasingly CER (vs. competitor)
- Decisions need often to be made in absence of perfect data
- Decisions have immediate consequences (vs. science)

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Therapeutic Risk Management

- Formal strategy to minimize known adverse drug reactions
- E.g.: avoid malformations in babies of women who use isotretinoin, thalidomide
- Based on
  - Narrow indication
  - Specific information
  - Contraception (abortion?)
  - Program evaluation
  - Problem areas: generics, patents

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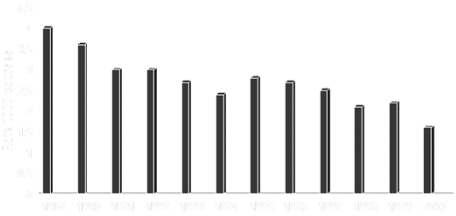
Pregnancy Rate per 1,000 person/courses of Accutane 1989-2000



Source: Allen Mitchell: Accutane Pregnancy Prevention Program; oral presentation ICPE 2007

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