What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

Brian L. Strom, MD, MPH

RBHS Chancellor

Executive Vice President for Health Affairs

March 11, 2016

Rutgers, The State University of New Jersey

Conflict of Interest Disclosure (1)

- Research grants provided by the US government, especially multiple different branches of the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality, Food and Drug Administration, the Department of Veterans Affairs, and the US Agency for International Development

- Research grants provided by foundations: American Cancer Society, American College of Cardiology, American College of Clinical Pharmacy Foundation, Asia Foundation, Charles A. Dana Foundation, Institute of Medicine of the National Academy of Sciences, Joint Commission on Prescription Drug Use, Pennsylvania Department of Health, Rockefeller Foundation, Andrew W. Mellon Foundation, and International Clinical Epidemiology Network, Inc.

- Research grants provided by private industry: Aetna, Alza Corp., Amgen, AstraZeneca, Bayer Corp., Bayer Consumer Care, Berlex Laboratories, Boran Pharmaceuticals, Bristol-Myers Squibb, the Burroughs Wellcome Company, Ciba-Geigy Corp., COR Therapeutics Inc., GlaxoSmithKline, Glaxo-SmithKline Beecham, Glaxo Wellcome, Health Information Designs, Inc., Hoechst-Roussel Pharmaceuticals, Hoffman-La Roche, Inc., Integrated Therapeutics, Inc., a subsidiary of Schering-Plough Corporation, International Formula Council, Key Pharmaceuticals Inc., Marion Merrell Dow, Inc., McNeil Consumer Products, McNeil Pharmaceuticals, Mead Johnson Pharmaceuticals, Merck and Company, Novartis Pharmaceuticals Corp., Pfizer Inc., Pfizer Pharmaceuticals, Pharming, PharMark Corp., A.H. Robins Company, Rowell Laboratories, Sandoz Pharmaceuticals, Schering Corp., Searle Pharmaceutical, Shire, Smith Kline and French Laboratories, Sterling Winthrop Inc., Syntex, Inc., Takeda Pharmaceuticals North America, the Upjohn Company, US Pharmacopeia, and Wyeth-Ayerst Research

- Pharmacoepidemiology training program support: NIH, Abbott Laboratories, Alza Corp., Amgen, Aventis Pharmaceuticals, Inc., Bayer Corp., Berlex Laboratories, Inc., Ciba-Geigy Corp., Genentech, Inc., Hoechst-Marion-Roussel, Inc., Hoffman LaRoche, Integrated Therapeutics Group, Inc., Johnson and Johnson, Mary E Groff Charitable Trust, Merck and Company, Inc., McNeil Consumer Product Company, McNeil Consumer Healthcare, Novartis Pharmaceuticals Corp., Pfizer Inc., Sanofi Aventis, Sanofi Pasteur, SmithKline Beecham Pharmaceuticals, Whitehall-Robins Healthcare, and Wyeth-Ayerst Research
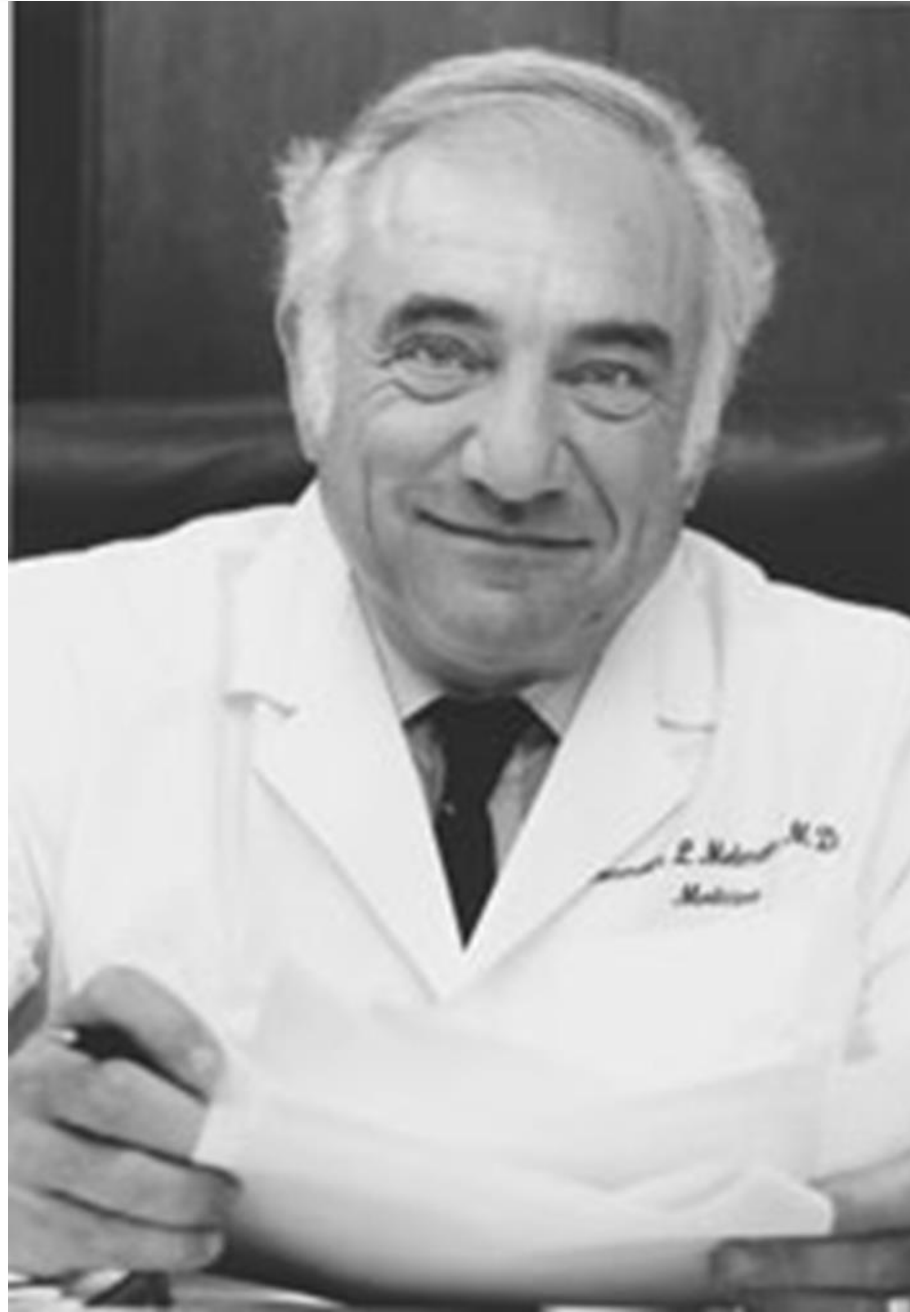
Conflict of Interest Disclosure (2)

- Consultant: Abbott Laboratories, AbbVie, Aetna, Alza Corp., Amgen, Astra-Merck, AstraZeneca LP, Aventis Pharmaceuticals, Bayer Corp., Berlex Laboratories, Biogen Idec, Boehringer Ingelheim, Bracco Diagnostics, Inc., Bristol-Myers Squibb Company, Centocor, Inc., Cephalon, Inc., Churchill Communications, Ciba-Geigy, Inc., Connaught Laboratories, CV Therapeutics, Cygnus Corp., Inc. , Daiichi Pharmaceuticals UK, Ltd., Dupont-Merck, Eli Lilly and Company, Ethicon, Endo Pharmaceuticals, Food and Drug Administration, GlaxoSmithKline, Hoechst-Roussel Pharmaceuticals, Inc., Hoffman LaRoche, IBEX Technologies Corp., IMS Health, Inflexxion, Inc., Inveresk Research North Carolina, Inc., IOM/National Academies of Science, Janssen Pharmaceuticals, John Wiley & Sons, Inc., LA-SER Europe Limited, Lexicon Pharmaceutical, Lundbeck LLC, McNeil Consumer Products Company, Mikalix and Company, Novartis, Omnicare, Inc., Orchid Bioscience, Inc., Oscient Pharmaceutical Corp., Otsuka, Pfizer, Inc., PharMark Corp., Pierre Fabre Dermatologie, Quintiles Strategic Research and Safety/The Lewin Group, Inc., Rhone Poulenc Rorer Pharmaceuticals, Inc., Roche Laboratories, Inc., RW Johnson Pharmaceutical Research Institute, Sanofi Pasteur, Inc., Schering-Plough Research Institute, Science, Toxicology, and Technology Consultants, Searle, Shire Pharmaceuticals, Syntex, USA, Inc., Takeda, TAP Pharmaceuticals, Teva Branded Pharmaceutical Products R&D, Inc., UCB Biosciences, Inc., Value Health Sciences, ViiV HealthCare, VIVUS, Inc., Warner Lambert, Wyeth Consumer Healthcare Division, and numerous law firms
- Member of the Board of Directors of Medco Health Solutions, Inc.

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you

- Introduction

- What makes pharmacoepidemiology different?

- Current approaches to pharmacoepidemiologic studies

- Historical examples from my experience

- Recent examples from my experience

- Selected lessons from a career in pharmacoepidemiology

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you
- Introduction
- What makes pharmacoepidemiology different?
- Current approaches to pharmacoepidemiologic studies
- Historical examples from my experience
- Recent examples from my experience
- Selected lessons from a career in pharmacoepidemiology

Brian Strom's Trainees: 1980-98

- Ravikiran Tamragouri (1980-82)
- Jeffrey Carson (1980-82)
- Jorge Soares (1982-83)
- Claudio Miranda (1983-84)
- Harold Feldman (1985-87)
- Walter Glender (1986-87)
- Rodolfo Rojo (1988-89)
- A. K. Dayal (1989-90)
- David Turner (1989-92)
- Su Kongpatanakul (1990-91)
- Francois Chapuis (1990-91)
- P. J. Brennan (1990-96)
- Sean Hennessy (1991-96)
- Shelley Sternberg (1991-94)

- Stephen Kimmel (1992-94)
- Robert O'Shea (1992-95)
- John Farrar (1993-2004)
- Mikkael Sekeres (1994-96)
- Mindy Schuster (1995-97)
- David Margolis (1995-2000)
- Tommaso Staniscia (1996-98)
- Robert Gross (1996-98)
- James Lewis (1996-98)
- Harry Seifert (1997-2000)
- Daniel Mines (1997-2000)
- Soledad Cepeda (1997-2000)
- Ebbing Lautenbach (1998-2005)

Brian Strom's Trainees: 1999-2015

- Jonathan Markowitz (1999-2002)
- Yu-Xiao Yang (2000-03)
- Philippe Szapary (2000-03)
- Jason Christie (2000-04)
- Gregory Bisson (2001-04)
- Worth Everett (2001-04)
- Edward Ochroch (2001-06)
- Vincent Lo Re III (2002-05)
- Charles Leonard (2003-11)
- Greg Armstrong (2004-06)
- Kevin Haynes (2005-07)
- Christopher Rowan (2005-10)
- Theoklis Zaoutis (2005-10)

- Pamela Weiss Fitch (2006-09)
- Jeffrey Gerber (2007-10)
- Stephen Keefe (2007-10)
- Janet McLaren (2008-10)
- Jessica Fishman (2008-12)
- Keri Donaldson (2009-11)
- D'Jahna Akinyemi (2009-12)
- Scott Halpern (2009-13)
- Robert Dood, Jr (2010-12)
- Angel Velarde Lopez (2011-14)
- Judd Flesch (2011-)
- Daniel Horton (2012-)
- Manuel Jimenez (2014-)

Other Penn Pharmacoepidemiology Trainees: 1981-2004

- Eddy Bresnitz (1981-85)
- David Roth (1992-94)
- Maria Leiva (1993-96)
- George Macones (1993-95)
- William Holmes (1995-97)
- Anne Blackwood (1995-97)
- Susan Krug-Gourley (1996-98)
- Mary Morrison (1996-98)
- Scott Kasner (1997-99)
- Liza O'Dowd (1997-2000)
- Long-Long Gao (1998-2000)
- Yiting Wang (1998-2000)
- Jonathan Kantor (1999-2001)

- Catherine Bradley (1999-2002)
- Anne Deitz (1999-2002)
- Elizabeth Hsia (1999-2004)
- Paul McGovern (2000-02)
- Darren Linkin (2001-03)
- Joel Gelfand (2002-04)
- Jon Burnham (1996-98)
- Adriana Izquierdo (2002-04)
- Athena Zuppa (2002-04)
- Esi Morgan DeWitt (2003-05)
- Samir Shah (2003-05)
- Leanne Beers Gasink (2003-06)
- Kenneth Katz (2004-06)

Other Penn Pharmacoepidemiology Trainees: 2004-09

- Babis Andreadis (2004-06)
- Lisa Collier Keller (2004-06)
- Sharon Meropol (2004-06)
- Jesse Pines (2004-06)
- Priya Gor (2004-07)
- Jason Kim (2005-07)
- Eric Pifer (2005-07)
- Timothy Beukelman (2005-07)
- Ingi Lee (2006-08)
- Jeffrey Munson (2006-10)
- Brian Fisher (2006-08)
- Eric Haas (2006-08)
- Tracey Wright (2006-08)

- Kelly Wade (2006-08)
- Kara Anthony Mascitti (2007-09)
- Shanu Kohli Kurd (2007-09)
- Rebecca Speck (2007-09)
- Seo Young Kim (2007-09)
- Pinyo Rattanaumpawan (2008-10)
- Sanjeev Swami (2008-10)
- David Olaleye (2008-11)
- Christopher Vinnard (2008-11)
- Tapan Maniar (2008-10)
- Daniel Dorgan (2009-11)
- Jeffrey Hafkin (2009-11)
- Jennifer Han (2009-11)

Other Penn Pharmacoepidemiology Trainees: 2009-15

- Melissa Lerman (2009-11)
- Timothy Gaulton (2010-12)
- Cara Hoffart (2010-12)
- Laurel Redding (2010-12)
- Rebecca Ruebner (2010-12)
- Alexis Ogdie-Beatty (2010-12)
- Jimish Mehta (2011-13)
- Junko Takeshita (2011-)
- Ami Desai (2011-14)
- Jason Freedman (2011-13)
- Todd Miano (2011-)
- Tamara Miller (2012-)
- Jennifer Wilkes (2012-15)

- Zelma Chiesa-Fuxench (2013-)
- Alysha Taxter (2013-15)
- Allison Tribble (2013-)
- Matthew Basiaga (2014-)
- Amanda DiNofia (2014-)
- Rana Hamdy (2014-)
- Karen James (2014-)
- Nathan Parker (2014-)
- Meijia Zhou (2014-)
- Megan Noe (2015-)

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you
- Introduction
- What makes pharmacoepidemiology different?
- Current approaches to pharmacoepidemiologic studies
- Historical examples from my experience
- Recent examples from my experience
- Selected lessons from a career in pharmacoepidemiology

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

"A desire to take medications is, perhaps, the greatest feature which distinguishes man from other animals."

Sir William Osler, 1891

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

"If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind , and all the worse for the fishes."

Oliver Wendell Holmes
Medical Essays, "Comments and Counter"
Currents in Medical Science

"Traditional" Pharmacoepidemiology Definition

- The study of the use and effects of drugs in populations

- Applies the methods of epidemiology to the content area of clinical pharmacology

Bench→ Bedside→ Population

Pharmacoepidemiology

pre-clinical

proof of concept

efficacy
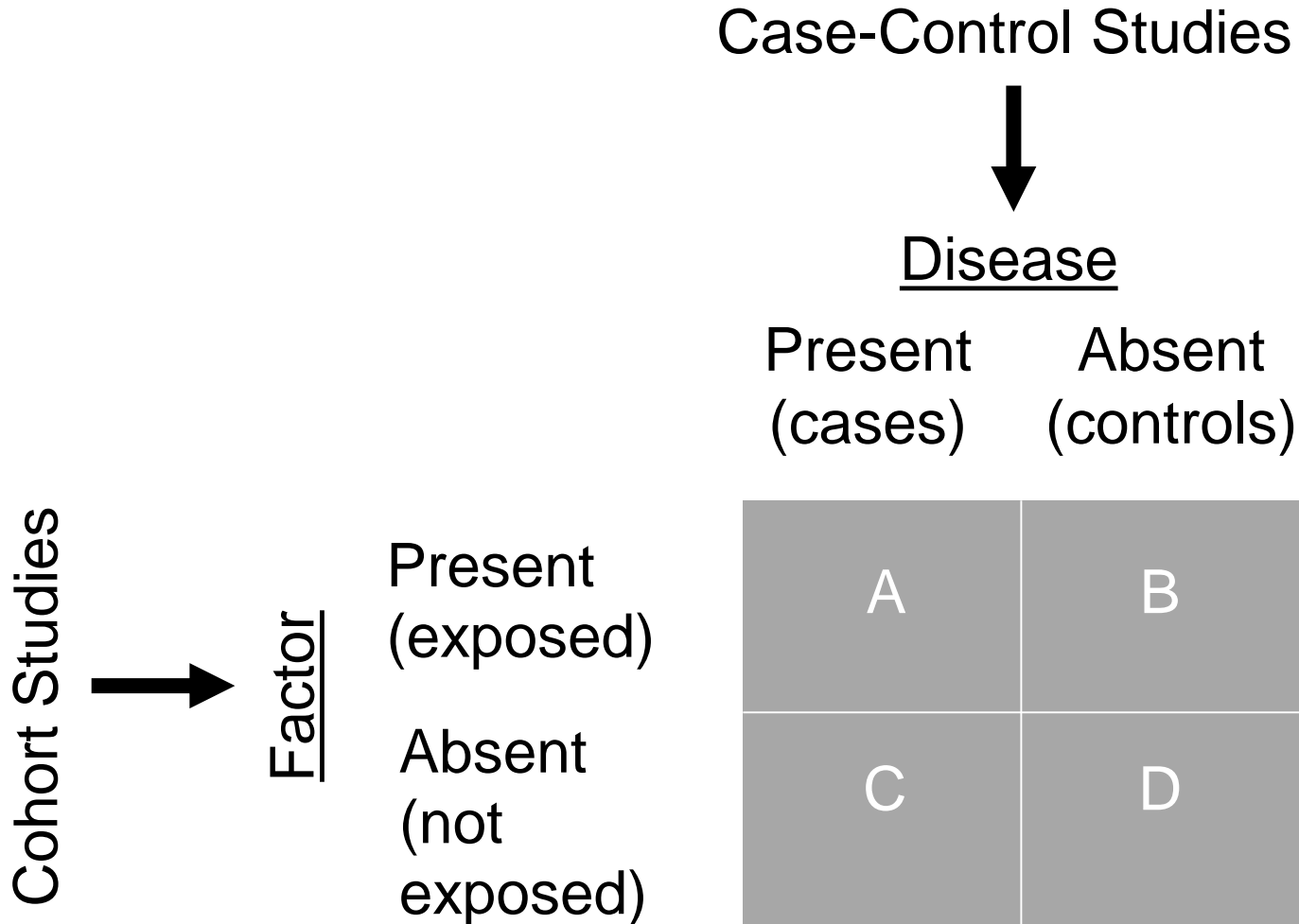
clinical effectiveness

effect of policies

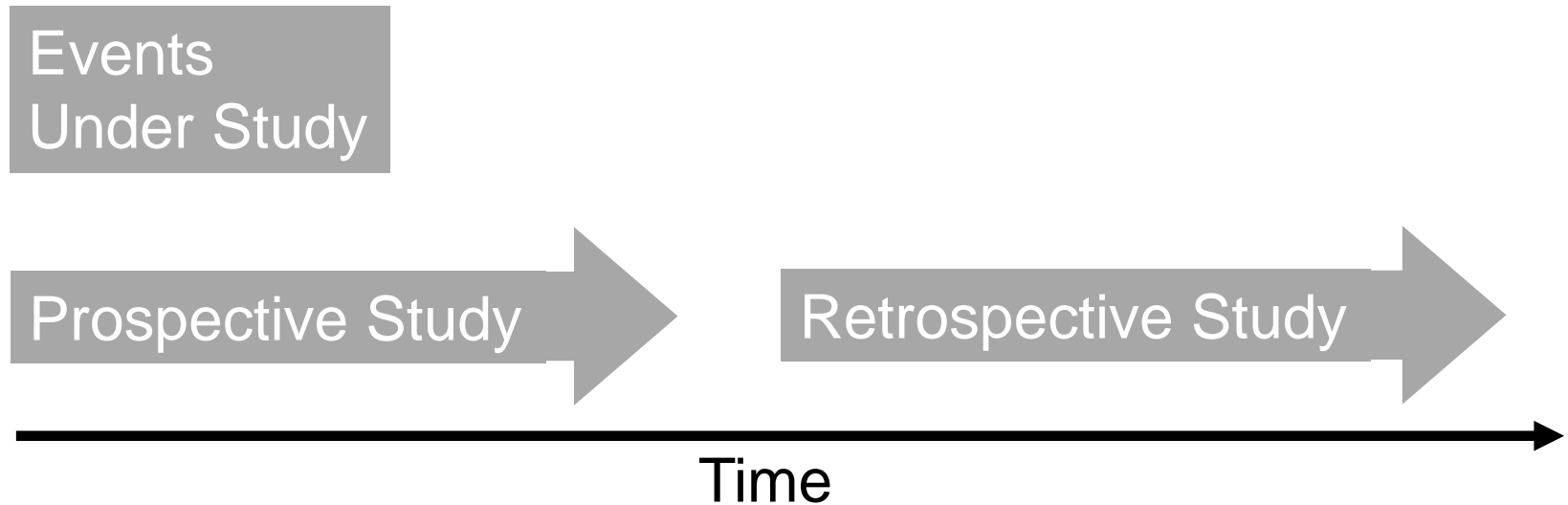# **Options in Research Design**

- **Analytic Studies**
  - Experimental Study
  - Prospective Cohort Study
  - Retrospective Cohort Study
  - Case-Control Study
- **Descriptive Studies**
  - Analyses of Secular Trends
  - Case Series
  - Case Reports

Options in Research Design

Options in Research Design

Prospective vs. Retrospective Studies

Limitations of Pre-Marketing Trials

- Carefully selected subjects may not reflect real-life patients in whom drug will be used
- Study subjects may receive better care than real-life pts
- Short duration of treatment
- No information on comparative effectiveness
- ⬆ development costs lead to ⬆ need for immediate huge sales ("blockbuster drugs"), and aggressive marketing
- DTC ads lead to over-use of the drug by patients for whom use of the drug is not compelling
- Yet, development programs with 3000 patients cannot reliably detect adverse events with an incidence of < 1 per 1000, even if severe
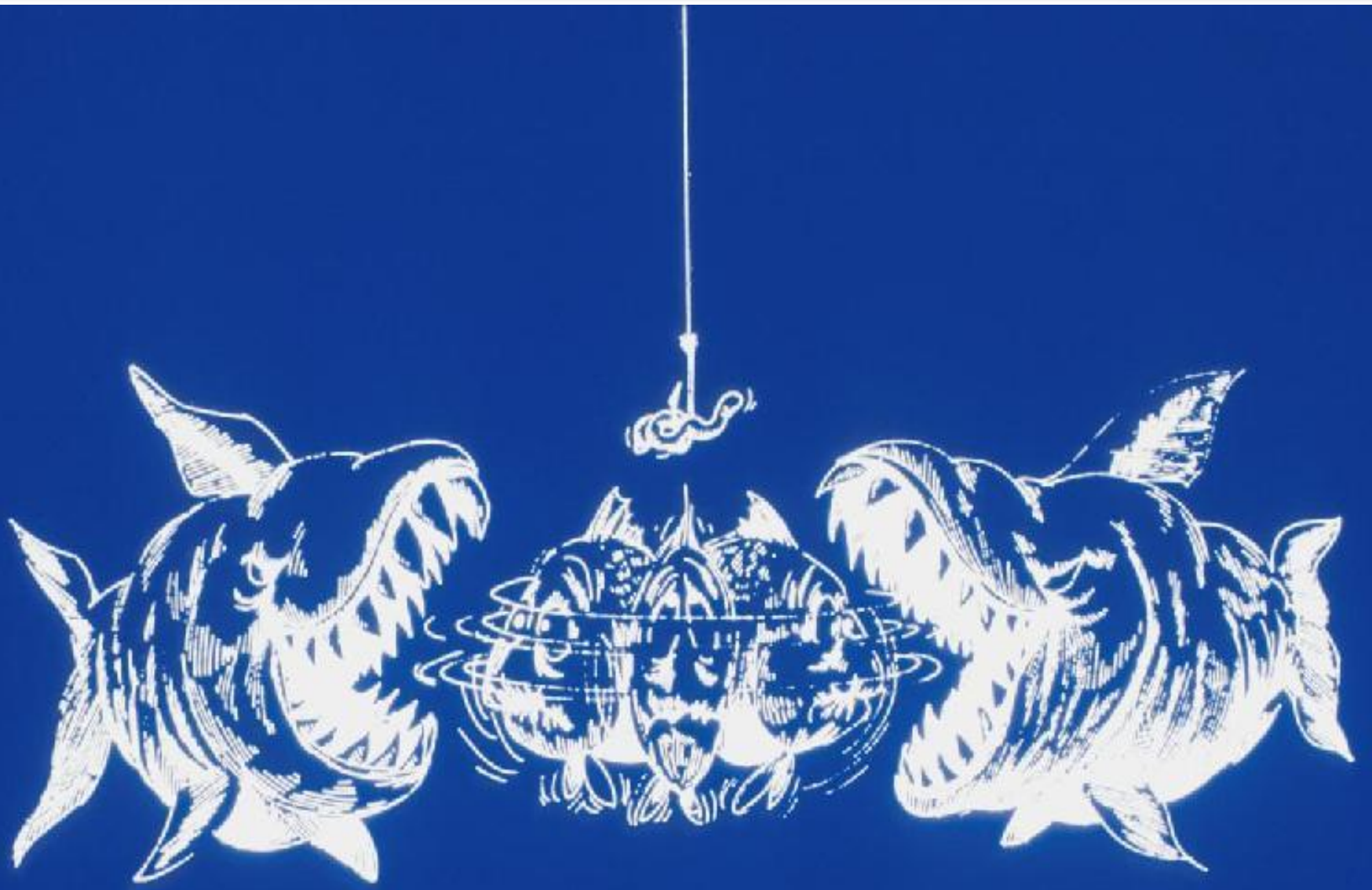
"Decisions usually involve risk."

© JOHNS HOPKINS Magazine

Net Effect

- Public misunderstands "safety": postmarketing discovery of drug ADR means someone "messed up"

- Increasing concern about the safety of our drugs

- Over-reaction leads to increased premarketing requirements with delayed access and drugs dropped from development
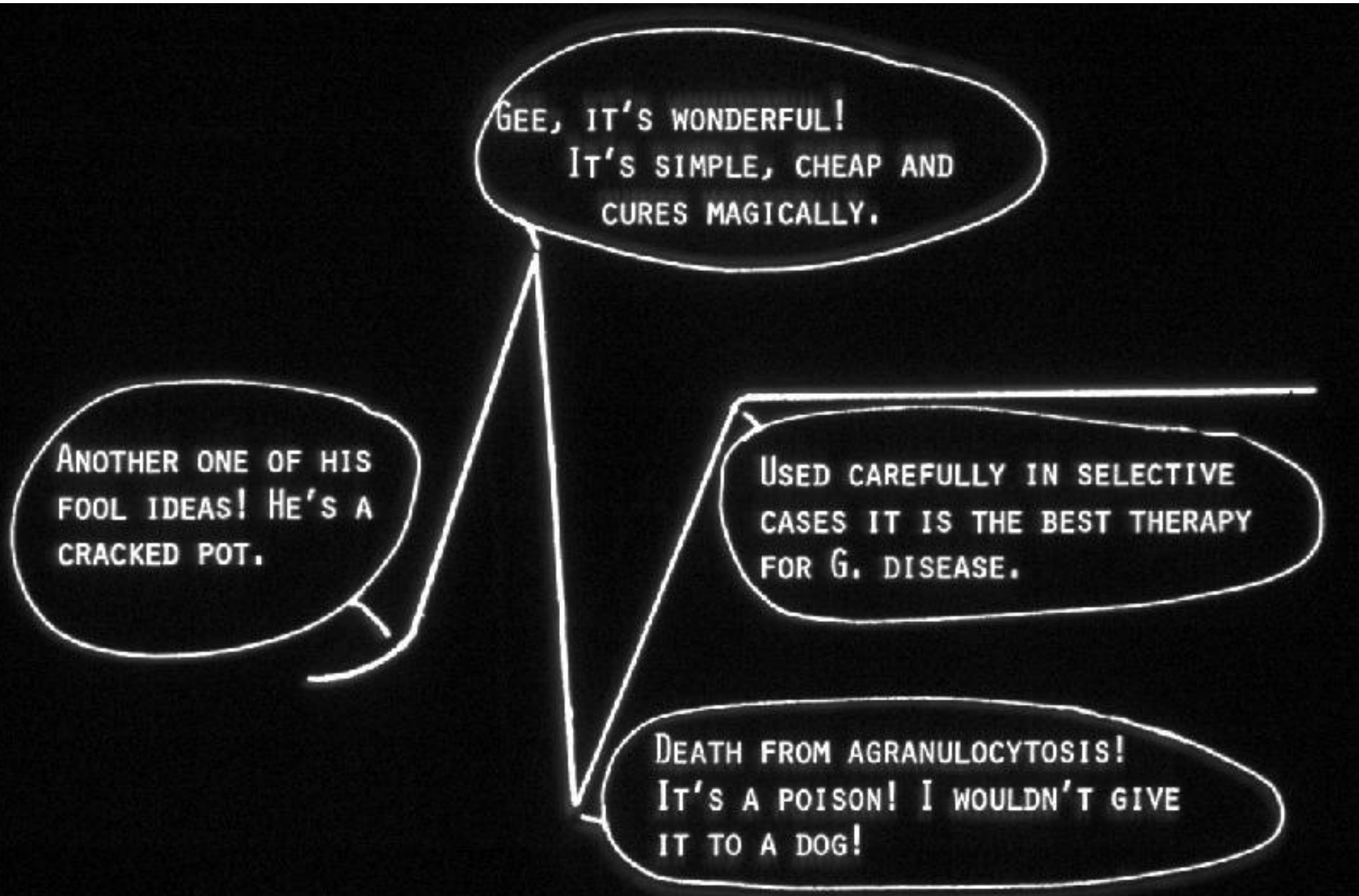
Oscillations in the development of a drug

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you
- Introduction
- What makes pharmacoepidemiology different?
- Current approaches to pharmacoepidemiologic studies
- Historical examples from my experience
- Recent examples from my experience
- Selected lessons from a career in pharmacoepidemiology

Pharmacoepidemiology: Unique Setting

- A large population needs to be studied
- Randomized clinical trials are less likely to be productive
- Answers often must be obtained quickly

Pharmacoepidemiology: Unique Characteristics of Methodologic Importance

- Exposure to drugs is not dichotomous
- Drug exposures have benefit
- Unlike most exposures of interest to epidemiologists, exposure to drugs is deliberate

Drawing by S. Harris, © 1979, The New Yorker Magazine, Inc.

Pharmacoepidemiology:
Other Unique Characteristics

- **Some studies can be very expensive**
- **Major role played by industry**
  - Premarketing studies
  - Funding for postmarketing studies
  - Contract Research Organizations (CROs)
- **Interplay of industry vs. regulators**
- **Enormous public interest in drug safety**
- **Rife with risk of conflict of interest**

Pharmacoepidemiology:
Methodologic Issues of Special Concern

- Measurement of exposure
- Confounding by indication/channeling

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you
- Introduction
- What makes pharmacoepidemiology different?
- Current approaches to pharmacoepidemiologic studies
- Historical examples from my experience
- Recent examples from my experience
- Selected lessons from a career in pharmacoepidemiology

Data Sources for Pharmacoepidemiologic Studies

- Spontaneous case reports of adverse reactions
- Aggregate population-based data sources
- Computerized collections of data from organized medical care programs
- Data collected for pharmacoepidemiology on an ongoing basis
- Existing data collected as part of other ad hoc studies
- Data collected de novo

Pharmacoepidemiology: Sources of Computerized Billing Data

Provider: Pharmacy

Provider: Hospital

Provider: Physician

Payor

Data User
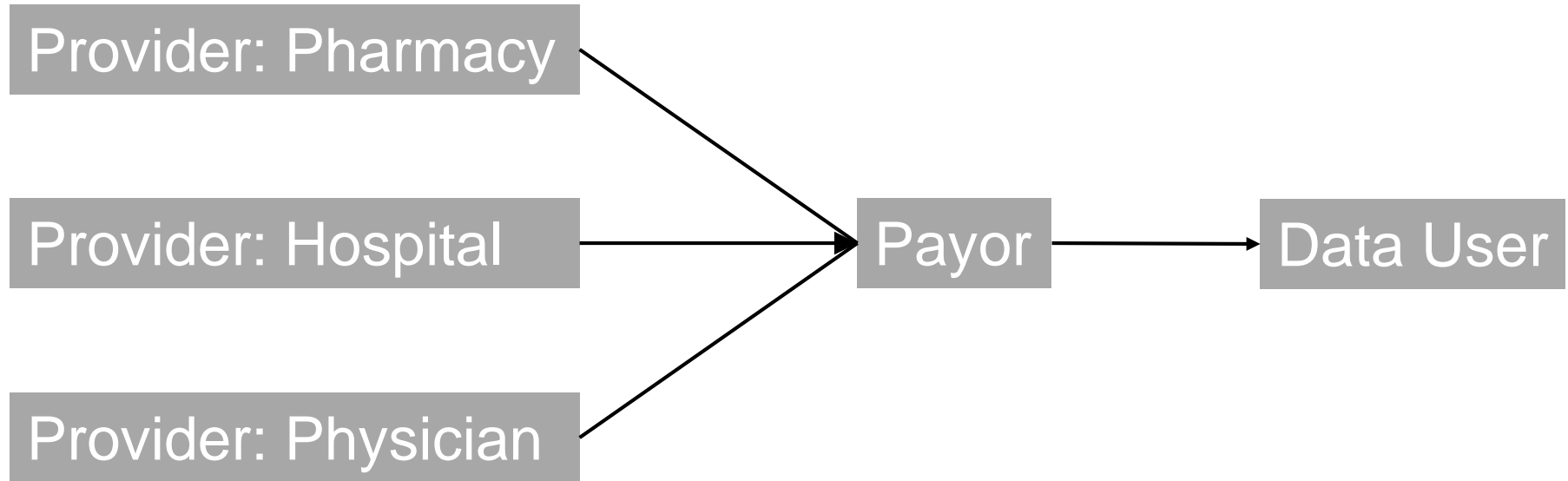
Use of Pharmacoepidemiology to Study Drug Mechanisms

- Risk factors for drug-induced disease

- Pharmacogenetics

- Molecular pharmacoepidemiology

- Epidemiologic study of drug interactions

"I've thrown in some prescription drugs that don't interact well."

Patient Safety and Medical Errors

- Iatrogenic injuries: up to 180,000 US deaths each year, and disability or prolongation of hospital stay in another 1.3 million

- Medical errors: 44,000 – 98,000 annual deaths, more than motor vehicle accidents, breast cancer, or HIV

- Medical errors: annual costs of $17-29B

Key Problem of "Historical" Pharmacoepidemiology

- Adverse drug events are the most common iatrogenic causes of patient injuries

- Most are the result of an exaggerated by otherwise usual pharmacological effect of the drug

- Yet, historically these have been ignored by pharmacoepidemiology, as they do not represent a focus of commercial and regulatory interest

"Less than one in ten thousand—something like one in fourteen thousand—gets these side effects. Hardly anybody gets these side effects. They're extremely rare. You should be very proud."

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you

- Introduction

- What makes pharmacoepidemiology different?

- Current approaches to pharmacoepidemiologic studies

- Historical examples from my experience

- Recent examples from my experience

- Selected lessons from a career in pharmacoepidemiology

Historical Examples from my Experience

- NSAIDs/GI Bleeding
- Suprofen/acute flank pain
- Endocarditis

Historical Examples from my Experience

- NSAIDs/GI Bleeding
- Suprofen/acute flank pain
- Endocarditis

NSAIDs/GI Bleeding: Aim

- To evaluate the risk of developing upper gastrointestinal (UGI) bleeding from nonsteroidal anti-inflammatory drugs (NSAIDs)

Carson JL, Strom BL, Soper KA, West SL, Morse ML. The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal bleeding. *Archives of Internal Medicine* 1987; 147:85-8.

NSAIDs/GI Bleeding: Methods

- Design: retrospective cohort study of Medicaid claims from Michigan and Minnesota

- Patients exposed to NSAIDS (47,136) were matched to unexposed patients (44,634)

- Potential confounding variables: age, sex, state, alcohol-related diagnoses at any time, anticoagulant exposure at any time, preexisting abdominal conditions, antacid and/or cimetidine exposure prior to NSAID exposure, corticosteroid exposure at any time, and indications for NSAID therapy

NSAIDs/GI Bleeding: Results

	Exposed Patients	Unexposed Patients
Number of Patients	47,136	44,634
Pts with UGIB per 10,000 Persons	155	96
Rate of UGIB per 10,000 Persons	33	22
Rate of UGIB per 10,000 Person Mos	1.27	0.83
Unadjusted Relative Risk (95% CI)	1.5 (1.2-2.0)	
Adjusted Relative Risk (95% CI)†	1.5 (1.1-1.9)	

† Adjusted for all potential confounding variables by logistic regression

Historical Examples from my Experience

- NSAIDs/GI Bleeding
- Suprofen/acute flank pain
- Endocarditis

Suprofen/Acute Flank Pain: Aim

- To explore the epidemiology of the unusual adverse reaction to suprofen: acute flank pain, often bilateral, sometimes with acute renal failure

Strom BL, Carson JL, Morse ML, West SL, Soper KA. The effect of indication on hypersensitivity reactions associated with zomepirac sodium and other non-steroidal anti-inflammatory drugs. *Arthritis and Rheumatism* 1987; 30:1142-8.

Suprofen/Acute Flank Pain: Methods

- Design: case-control study
- Cases: the 163 individuals reported to the spontaneous reporting system
- Controls: 4 patients treated with suprofen by the same prescribers, who did not develop the flank pain syndrome
- Data collection: questionnaires completed by the prescribers

Suprofen/Acute Flank Pain: Results

- Risk factors include: male sex, other allergies, and participation in exercise (especially Nautilus)

- Probable risk factors include: concurrent ibuprofen, concurrent acetaminophen (protective), recent increase in sun exposure, recent increase in activity, and recent change in alcohol intake

- Possible risk factors include: pre-existing renal disease, kidney stones, gout, and living in the sun belt

- Most risk factors are consistent with the pathogenic mechanism postulated: acute short-term diffuse crystallinization of uric acid in renal tubules

Historical Examples from my Experience

- NSAIDs/GI Bleeding
- Suprofen/acute flank pain
- Endocarditis

Risk Factors for Endocarditis: Aim

- To determine the risk factors associated with the development of infective endocarditis
  - Host factors (especially mitral valve prolapse)
  - Procedures (especially dental treatment)

Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, Levison ME, Korzeniowski OM, Kaye D. Dental and cardiac risk factors for infective endocarditis: a population-based case-control study. *Annals of Internal Medicine* 1998; 129:761-9.

Risk Factors for Endocarditis: Study Design

- Case-control study: cases of endocarditis compared to community-based controls

Results: Previous Heart Disease
(N = 273 cases, 273 controls)

Variable	Exposed Cases	Exposed Controls	Adjusted OR (95% CI)
Any cardiac valve abnl	112	17	12.8 (6.1 – 27)
Mitral valve prolapse	58	6	24.3 (6.4 – 91)
Congenital heart disease	26	7	4.1 (1.2 – 13)
Cardiac valve surgery	37	2	17.0 (2.5 – 117)
Rheumatic fever w/heart	17	4	5.1 (0.5 – 50)
Previous endocarditis	17	1	17.6 (2.2 – 138)
Other valve disease	14	1	8.4 (0.83 – 85.6)
Heart murmur w/o valve	63	14	8.2 (3.5 – 19.3)

Results: Dental Procedures
(N = 273 cases, 273 controls)

Prior Dental Procedure (90 days)	Exposed Cases	Exposed Controls	Adjusted OR (95% CI)
Any dental procedure	63	64	1.1 (0.54 – 2.09)
Any invasive procedure	27	26	1.3 (0.50 – 3.28)
Prophylaxis	33	33	1.1 (0.43 – 2.96)
Filling	17	27	0.9 (0.29 – 2.84)
Periodontal treatment	14	14	1.0 (0.26 – 3.55)
Restorative dentistry	4	9	0.3 (0.04 – 1.86)
Extraction	8	4	8.1 (0.77 – 84.9)
Root canal treatment	5	6	2.0 (0.26 – 15.8)
Treatment of abscess	1	2	0.1 (0.00 – 103)
Mouth or gingival surg	1	1	1.0 (0.06 – 16.0)
Other dental procedures	8	3	6.9 (0.63 – 75.6)

Risk Factors for Endocarditis: Results

- Among those with a history of cardiac valvular abnormality, the results for dental procedures were similar: 27.7% of cases vs. 35.3% of controls

- Among those with oral flora, the results for dental procedures were similar

- Odds ratios for dental procedures were not affected by the use of prophylactic antibiotics

- Only 31 (11.0%) cases had both cardiac lesions and dental treatment within 90 days

- Only 18 (11.6%) cases infected with oral flora had both cardiac lesions and dental treatment within 90 days, representing only 6.6% of all cases; 10 of these had received prophylactic antibiotics

Risk Factors for Endocarditis: Conclusions

- Even if antibiotics were 100% effective, only a very small proportion of cases of this uncommon condition could be prevented by the then policy of widespread use of prophylactic antibiotics for dental procedures; a maximum of 1.3 cases/1,000,000/year would be prevented

- Antecedent dental work does not seem to be a risk factor for endocarditis

- Widespread practice of prophylactic antibiotics for those with cardiac abnormalities undergoing dental treatment should be reconsidered

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you
- Introduction
- What makes pharmacoepidemiology different?
- Current approaches to pharmacoepidemiologic studies
- Historical examples from my experience
- Recent examples from my experience
- Selected lessons from a career in pharmacoepidemiology

Recent Examples from my Experience

- Ziprasidone vs. Olanzapine
- Statins

Recent Examples from my Experience

- Ziprasidone vs. Olanzapine
- Statins

Comparative Mortality Associated with Ziprasidone vs. Olanzapine in Real World Use: Aim

- To determine if the use of ziprasidone in the "real world" increases the risk of clinically meaningful, serious cardiovascular events

Strom BL, Eng SM, Faich GA, Reynolds RF, D'Agostino RB, Ruskin J, Kane JM. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: the ziprasidone observational study of cardiac outcomes (Zodiac). *American Journal of Psychiatry.* 2011; 168:193-201.

Comparative Mortality Associated with Ziprasidone vs. Olanzapine in Real World Use: Methods

- Large, naturalistic, prospective study with random assignment of patients to antipsychotic treatment, to control for channeling bias

- 18,000 patients randomized to ziprasidone or olanzapine

- No additional study-required monitoring or tests after randomization

- Follow-up during usual care for one year

Mortality Endpoint Results

Mortality Endpoint	Ziprasidone (n=9,077) n (%)	Olanzapine (n=9,077) n (%)	RR (95% CI)	Total (n=18,154) n (%)
Non-suicide mortality*	83 (0.91)	81 (0.90)	1.02 (0.76, 1.39)	164 (0.90)
All cause mortality	103 (1.13)	102 (1.12)	1.01 (0.77, 1.33)	205 (1.13)
Sudden death	2 (0.02)	3 (0.03)	0.67 (0.11, 3.99)	5 (0.03)
CV mortality†	3 (0.03)	8 (0.09)	0.38 (0.10, 1.41)	11 (0.06)
Suicide mortality	19 (0.21)	16 (0.18)	1.19 (0.61, 2.31)	35 (0.19)

*One death in the ziprasidone group met criteria for both non-suicide and suicide mortality. patients were in the hospital
† When events classified by EC as cardiovascular mortality with insufficient data conservatively added to definite and possible events, RR = 1.60 (95% CI: 0.84, 3.05) for ziprasidone vs. olanzapine.

Hospitalization Endpoint Results

Hospitalization Endpoint[‡]	Ziprasidone (n=9,077) n (%)	Olanzapine (n=9,077) n (%)	RR (95% CI)
All-cause hospitalization	1370 (15.1)	987 (10.9)	1.39 (1.29, 1.50)
Hospitalization for arrhythmia, MI, or DKA	24 (0.3)	20 (0.2)	1.20 (0.66, 2.17)
Hospitalization for arrhythmia	7 (0.1)	4 (0.0004)	1.75 (0.51, 5.98)
Hospitalization for myocardial infarction	13 (0.1)	11 (0.1)	1.18 (0.53, 2.64)
Hospitalization for diabetic ketoacidosis	5 (0.1)	5 (0.1)	1.00 (0.29, 3.45)

‡ Hospitalization endpoints include events that occurred or were identified via diagnostic tests or procedures (e.g. ECGs) carried out while patients were in the hospital

Comparative Mortality Associated with Ziprasidone vs. Olanzapine in Real World Use: Conclusions

- Ziprasidone and olanzapine not different on non-suicide mortality primary endpoint

- Risk of mortality or hospitalization due to MI and arrhythmia events not significantly different between ziprasidone and olanzapine

- All cause hospitalization greater with ziprasidone than olanzapine, but not for CVD or diabetes

- Suggests that modest QTc prolongation with ziprasidone does not translate into an elevated risk of non-suicide mortality compared with olanzapine

Recent Examples from my Experience

- Ziprasidone vs. Olanzapine
- Statins

Statin Therapy and Risk of Acute Memory Impairment: Specific Aim

- Investigate the association between the use of statins and diagnosed acute memory impairment

Strom BL, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin therapy and risk of acute memory impairment. *JAMA Intern Med.* 2015 Aug;175(8):1399-405.

Statins: Previously Published Safety Data (1)

- **Real-world safety data on memory effects are inconclusive, even contradictory**
    - Case reports & case series suggest acute adverse effects of statins on memory; challenge-rechallenge reports strongly suggest that the acute effects of statins on memory can be real and reversible
    - Controlled observational studies and clinical trials show either improved memory associated with use of statins or no difference between users and non-users
    - Recent meta-analysis shows a benefit from statins in preventing Alzheimer's disease and all-type dementia

Statins: Previously Published Safety Data (2)

- **Contradictory reports on the association between statins and memory impairment may be due to:**
  - Duration of follow-up (short term vs long term memory)
  - Different drugs being tested
  - Same drug could have different effects in different pts
  - Limited sample size
  - Differences in how memory was measured
  - Dose
  - Choice of controls
  - Control for confounding

Study Design (1)

- **Retrospective cohort study**
  - New users of statin medications vs:
    - o unexposed controls
    - o users of non-statin lipid lowering drugs (LLDs), to help reduce the possibility of confounding by indication and detection bias
- **Index date: first exposure to LLD or for unexposed, index date of the exposed subject in the matched pair**

Study Design (2)

- **Secondary case-crossover study**
  - To eliminate confounding by stable patient factors
  - For each patient diagnosed with acute memory loss, the presence/absence of prior exposure to statins during days 0-30 immediately preceding the first diagnosis of acute memory loss was compared to the presence of statin exposure during three earlier control periods preceding the diagnosis of memory loss

Data Source

- The Health Improvement Network (THIN), a database composed of primary medical records (nearly 11 million) from physician providers (553) in the UK
- Data collected during 1980 through January 2012

Selection of Study Patients

	Primary Study Group	Primary Control Group	Second Control Group
Index Drug	New rx statins	Nonusers of any LLDs	New rx non-statin LLDs
Propensity Score Matching Criteria	1:1 matched pairs		No matching (small numbers)
	GP practice, sex, age-group at start, duration of enrollment		
Exclusions	None		Prior statin use
Rationale			Control for selection bias, difference in risk between drug classes

Study Outcome

- **Onset of acute, reversible memory impairment**
- **To examine the validity of the diagnosis:**
  - GPs of 100 randomly selected patients coded for acute memory loss received a questionnaire requesting confirmation of diagnosis, disease onset, and whether it resolved within three months
  - Requested free text comments from electronic medical records of GPs for 1000 patients with dx

Comparisons

- Primary comparison: statin users vs matched non-users of any LLDs
- Secondary comparison: statin users vs. unmatched users of non-statin LLDs
- Sub-analysis comparing non-statin LLDs vs. matched non-user controls

Results: Number of Patients with Incident Acute Memory Loss after First Exposure

Time Period	Statin Users OR (95% CI) n=482,543	Matched Non-Users of any LLDs OR (95% CI) n=482,543	Unmatched Users of Non-Statin LLDs OR (95% CI) n=26,484
0-30 days after first exposure	376 (0.08%)	114 (0.02%)	18 (0.07%)

Results: Acute Memory Loss with Statins

Time Period	Statins vs. Non-Users Adjusted OR (95% CI) (conditional logistic regression)		Statins vs. Users of Non-Statin LLDs Adjusted OR (95% CI) (ordinary logistic regression)	
	Adjusted for matching variables	Adjusted for matching and all other confounding variables	Adjusted for sex, age-group, and enrollment duration	Adjusted for matching and all other confounding variables
0-30 days after 1st exposure	3.30 (2.67, 4.07)	4.40 (3.01, 6.41)	1.01 (0.63, 1.62)	1.03 (0.63, 1.66)

Results: Odds Ratio (95% CI)
Acute Memory Loss with Non-Statin LLDs

Time Period	Number of Patients with Incident Acute Memory Loss after 1st Exposure		Adjusted OR (95% CI) (conditional logistic regression)	
	Users of non-statin LLDs n=26,484	Matched non-users of any LLDs n=26,484	Adjusted for matching variables	Adjusted for matching and all other confounding variables
0-30 days after 1st exposure	18 (0.07%)	5 (0.02%)	3.60 (1.34-9.70)	NA[*]

[*]The fully adjusted model could not converge owing to small numbers

Conclusions

- Both statin and non-statin LLDs were strongly associated with acute memory loss in the first 30 days following exposure when compared to nonusers, but not when compared to each other

- Either all LLDs cause acute memory loss, regardless of drug class, or the association is due to detection bias rather than a causal association

What are Our Drugs Truly Doing to Our Patients? Lessons from Pharmacoepidemiology

- Thank you

- Introduction

- What makes pharmacoepidemiology different?

- Current approaches to pharmacoepidemiologic studies

- Historical examples from my experience

- Recent examples from my experience

- Selected lessons from a career in pharmacoepidemiology

Selected Lessons from a Career in Pharmacoepidemiology

- **For the clinical epidemiologist:**
  - Drugs are different from other exposures
  - Don't ignore or forget mechanism
  - Be a database user, not a database builder
- **For other clinical pharmacologists:**
  - Denominators are key; the plural of anecdote is not data
  - Data quality is paramount—don't analyze noise
  - Sample size does not make up for poor study design; one can have a very precise measure of a wrong answer
  - Don't lose rigor, in seeking innovation
  - The question is, what is the question?

Selected Lessons from a Career in Pharmacoepidemiology

- **For all:**
  - Choose carefully, your collaborators, your trainees, and especially your family