Introduction to Pharmacoepidemiology

Dr. Kwame Appenteng

5th MURIA Workshop/Symposium

July 2019

Course Overview: Monday July 8, 2019

Time	Topic
9:00 - 10:45	Introduction to Pharmacoepidemiology (PE)
11:15 – 13:00	Research Methodology
13:45 - 15:30	Data Sources for PE Research
16:00 - 17:45	Class Exercises

Course Overview: Tuesday July 9, 2019

Time	Topic
9:00 - 10:45	Bias in PE studies
11:15 – 13:00	Pharmacovigilance and drug safety in PE
13:45 - 15:30	Drug utilization research in PE
16:00 - 17:45	Class Exercises

Faculty

- Kwame Appenteng
- Alison Bourke
- Francis Kalemeera
- Joseph Fadare

Outline

- What is Pharmacoepidemiology?
- Role within Pharmacovigilance
- Observational Research
  - Guidelines
  - Key Initiatives/Activities
- Pharmacoepidemiology – Key Challenges
- Case Examples
  - Cohort Design
  - Case Control Design

What is Pharmacoepidemiology?

Why?

- The need to use observational methodology in the evaluation of medical products

How?

- Epidemiologic methods
- Clinical knowledge
- Basic science

Covers all medical products

- Drugs, vaccines, and medical devices

Pharmacoepidemiology

What is Pharmacoepidemiology?

The study of the use of and the effects of drugs in large numbers of people. A joining of clinical pharmacology (content area) and epidemiology (methodology).

Source: Strom BL and Kimmel SE, eds. Textbook of *Pharmacoepidemiology*. John Wiley & Sons, Hoboken, NJ, 2006.

What is Pharmacoepidemiology? (con't)

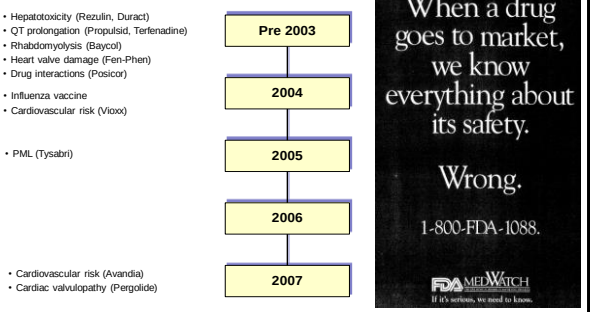
From the ISPE website
https://www.pharmacoepi.org/about/index.cfm

"Pharmacoepidemiology may be defined as the study of the utilization and effects of drugs in large numbers of people. To accomplish this study, pharmacoepidemiology borrows from both pharmacology and epidemiology. Thus, pharmacoepidemiology can be called a bridge science spanning both pharmacology and epidemiology."

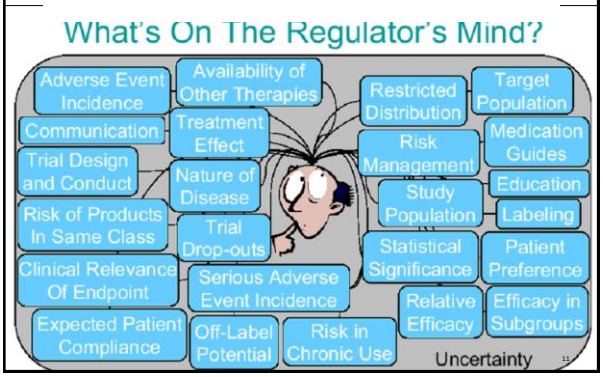
Pharmacoepidemiology: A public health perspective

- Not only providing scientific evidence
  - Not only publishing a peer-reviewed article
- Epidemiology findings provide actionable evidence
  - Support medical product development
  - Support regulatory decisions
  - Support reimbursement decisions
  - Prevent / control public health disaster
- (Therapeutic) Risk Management
  - Maximize benefit, minimize risk

Major Patient Safety Issues / Withdrawals



What's in the Regulator's Mind?



What is Pharmacovigilance?

"all scientific and data gathering activities relating to the detection, assessment and understanding of adverse events. This includes the use of pharmacoepidemiological studies".

(FDA – Guidance for Industry, 2005)

"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. Encompasses the use of pharmacoepidemiological studies".

(ICH E2E)

The Role of Pharmacovigilance

These activities are undertaken with the goal of identifying adverse events and understanding their nature, frequency, and potential risk factors

The goal of pharmacovigilance is to closely monitor the safe use of pharmaceutical products by exercising surveillance of product use throughout the lifecycle of the product.

Pharmacovigilance principally involves the identification and evaluation of safety signals

Safety Signal - Definition

Safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use.

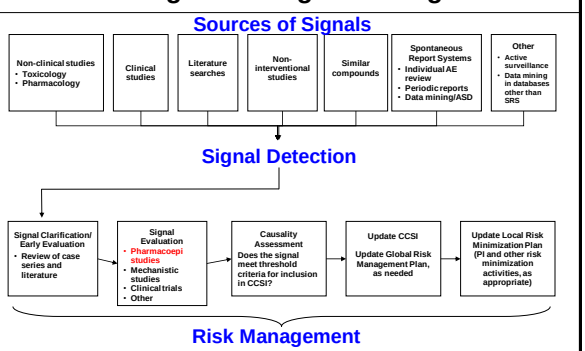
Source:

- Preclinical data, Clinical data, and Post-marketing data

Can a single case report be viewed as a signal?

Yes, It is possible that even a single well documented case report can be viewed as a signal (positive rechallenge).

Pharmacovigilance: Signal Management



Limitations of Post-Marketing Reporting System

- Under-reporting of suspected events
- Incomplete information – difficulty in assessing causality
- Reporting bias
- Lack of denominator – extremely difficult to accurately determine exposure

Evidence Hierarchy
RCTs Versus Observational Studies

Lower degree of uncertainty
(e.g. causality, incidence)

- Clinical trials
- Observational studies
- Individual case reports

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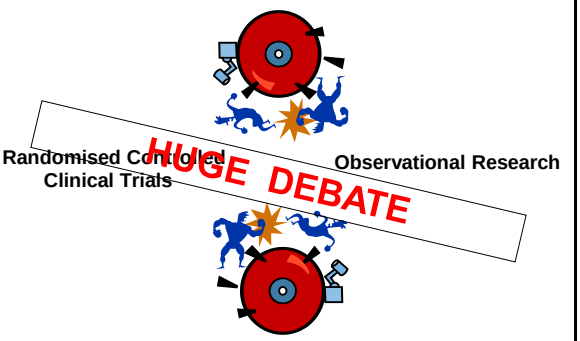
What About the Evidence Hierarchy?



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Where Observational Research Can Add Value

- Disease progression and risk factors
- Patterns of usual clinical care
- Real world effectiveness & safety of therapy
- Naturalistic clinical and economic outcomes
- Patient reported outcomes
- Outcomes that are rare or which occur only after prolonged therapy
- Interventions that are not amenable to a controlled experiment.....

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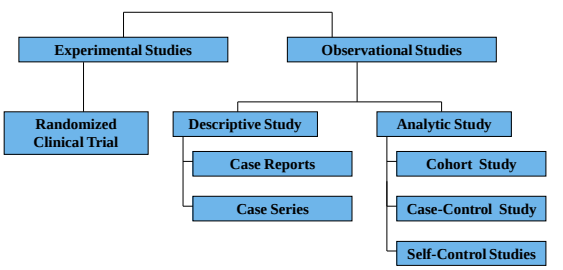
Study Designs



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Increasing Observational Research Guidelines and Activities

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PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2008; 17: 200–208
Published online 17 September 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1471

ISPE COMMENTARY

Guidelines for good pharmacoepidemiology practices (GPP)†

INTRODUCTION

Pharmacoepidemiologic studies provide valuable information about the health effects of healthcare products. The ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) are intended to assist investigators with issues pertaining to the planning, conduct, and evaluation of pharmacoepidemiologic research. health-related behaviors. Pharmacoepidemiology is the scientific backbone of therapeutic risk management—the process of assessing a product's benefits and risks, and developing, implementing, and evaluating strategies to enhance the overall balance of such benefits and risks. These guidelines are intended to address these activities and other pharmacoepidemiologic studies.

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STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants (b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding

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U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

FDA Amendments Act of 2007

Section 905: Active Postmarket Risk Identification and Analysis

- Establish a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including
  - at least 25,000,000 patients by July 1, 2010
  - at least 100,000,000 patients by July 1, 2012
- Access a variety of sources, including
  - Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs)
  - Private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data)

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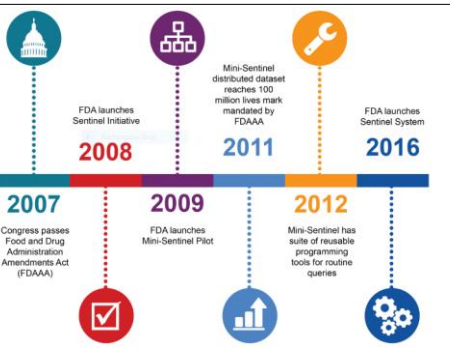
What is the FDA sentinel initiative?

- FDA's Sentinel Initiative is a long-term effort to create a national electronic system for monitoring FDA-regulated medical products.
- The Sentinel System includes the Active Post-market Risk Identification and Analysis (ARIA) system mandated by US Congress in the FDA Amendment Act (FDAAA) of 2007.
- The Sentinel Initiative created focused surveillance efforts around vaccine safety using the Post-market Rapid Immunization Safety Monitoring (PRISM) system, and supports regulatory review of blood and blood products with its Blood Surveillance Continuous Active Network (BloodSCAN).
- Mini-Sentinel was a pilot program launched by the FDA in 2009 to test the feasibility of the Sentinel Initiative, and to develop scientific approaches needed for creating such a national system.
- In 2014, the FDA started transitioning from Mini-Sentinel pilot to the fully operational Sentinel System.
- FDA launched the Sentinel System in 2016.

Sources: [1]Ball et al (2016); [2]Sentinel (2017): https://www.sentinelinitiative.org/background

FDA's Sentinel Initiative



OHDSI

OBERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

- A multi-stakeholder, interdisciplinary collaborative initiative to bring out the value of health data through large-scale analytics
- An international network of researchers and observational health databases with a central coordinating center housed at Columbia University
- Research community: multiple disciplines (e.g., clinical medicine, biostatistics, computer science, epidemiology, life sciences)
- Stakeholder groups (e.g., researchers, patients, providers, payers, product manufacturers, regulators).

OHDSI

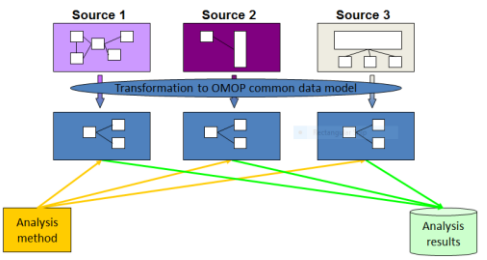
OBERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

- Focus areas:
  - Data standardization, Medical product safety surveillance, Comparative effectiveness research, Personalized risk prediction, Data characterization, Quality improvement
- Software
  - ATLAS – a web-based integrated platform for database exploration, standardized vocabulary browsing, cohort definition, and population-level analysis
  - ACHILLES – a standardized database profiling tool for database characterization and data quality assessment

OHDSI

OBERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

OMOP Common Data Model



https://www.ohdsi.org/

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

What is ENCePP?

- The **European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)** is an initiative that **brings together expertise and resources** in pharmacoepidemiology and pharmacovigilance across Europe. ENCePP is coordinated by the European Medicines Agency.
- ENCePP aims to **strengthen the monitoring of the benefit:risk balance of medicinal products**. This will be achieved by facilitating the conduct of **high quality, multi-centre, independent post-authorisation studies (PAS)** with a focus on observational research.
- ENCePP is comprised of research centres and networks referred to as '**ENCePP partners**'. Participation in ENCePP is voluntary.
- ENCePP is **globally acknowledged** for its expertise and outputs.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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Who are the ENCePP partners?

Centres (>150)
- Public (university, hospital, government, charities)
- Others (CROs, consultants)

Networks (>20)
- International
- National

Special interests: psychiatry, rheumatology, respiratory, effectiveness, teratology, pharmacogenetics, congenital abnormalities, women's health, paediatrics, psoriasis, severe cutaneous adverse reactions to drugs;

Data sources (>50)

http://www.encepp.eu/

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

What ENCePP offers to industry

ENCePP supports the conduct of **high quality industry-funded post-authorisation studies (PAS)** by:

- Supporting the conduct of **joint studies** by facilitating collaborations;
- Providing opportunities to participate, through consultations, in the development of **pharmacoepidemiological research standards and methods** for the post-authorisation safety surveillance of medicinal products;
- Developing and maintaining **methodological, transparency and governance tools** for the planning, design, conduct and reporting of studies according to standards recommended in the EU Good Pharmacovigilance Practices (GVP).
- Giving access to dedicated tools for the conduct of studies:
  - **ENCePP Resources Database** for research centres and data sources;
  - **EU PAS Register** for the registration of PAS with focus on observational research.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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- A partnership between the EU and the European pharmaceutical industry.
- The world's biggest public-private partnership (PPP) in the life sciences
- Originated from the European Technology Platform (ETP) on Innovative Medicines that was supported under the European Commission's Sixth Framework Programme for Research (FP6), from 2005 to 2009
- Following discussions in the European Parliament and among the Member States, the legislation creating IMI was approved in December 2007.

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- The overall goal of the IMI1 program was to significantly improve the efficiency and effectiveness of the drug development process with the long-term aim that the pharmaceutical sector produce more effective and safer innovative medicines.
- The main goal of IMI2 (2014-2020), is to develop next generation vaccines, medicines and treatments, such as new antibiotics
- There are multiple projects and working groups in IMI
- For more information visit: https://www.imi.europa.eu/

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ADVANCE

Accelerated development of vaccine benefit-risk collaboration in Europe

Ongoing | IMI1 | Infectious diseases, Vaccines, Methods for benefit/risk assessment

FLUCOP

Standardization and development of assays for assessment of influenza vaccines correlates of protection

Ongoing | IMI1 | Respiratory diseases, Infectious diseases, Vaccines

PROTECT

Pharmacoepidemiological research on outcomes of therapeutics by a European consortium

Closed | IMI1 | Tools for predicting/monitoring efficacy, Methods for benefit/risk assessment

STEMBANCC

Stem cells for biological assays of novel drugs and predictive toxicology

Closed | IMI1 | Diabetes & metabolic disorders, Psychiatric diseases, Stem cells

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Pharmacoepidemiology: Key Challenges

- Identification of Sufficient Data Source
  - Sample Size
  - Generalizability
- Validation
  - Exposure
  - Outcome
- Establishing Causality
  - Chance
  - Bias
  - Confounding

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Cohort - Example

Research letters

COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease

Wayne A Ray, C Michael Stein, James R Daugherty, Kathi Hall, Patrick G Arbogast, Marie R Griffin

Results of premarketing and postmarketing trials have raised doubts about the cardiovascular safety of the non-steroidal anti-inflammatory drug (NSAID) rofecoxib, especially at doses greater than 25 mg. Between Jan 1, 1999, and June 30, 2001, we did a retrospective cohort study of individuals on the expanded Tennessee Medicaid programme (TennCare), in which we assessed occurrence of serious coronary heart disease (CHD) in non-users (n=202 916) and in users of rofecoxib and other NSAIDs (rofecoxib n=24 132, other n=151 728). Participants were aged 50–84 years, lived in the community, and had no life-threatening non-cardiovascular illness. Users of high-dose rofecoxib were 1·70 (95% CI 0·98–2·95, p=0·058) times more likely than non-users to have CHD; among new users this rate increased to 1·93 (1·09–3·42, p=0·024). By contrast, there was no evidence of raised risk of CHD among users of rofecoxib at doses of 25 mg or less or among users of other NSAIDs.

Lancet 2002; **360:** 1071–73

The results of VIGOR,[1] a large clinical trial, indicated that individuals who took rofecoxib 50 mg were five times more likely to have a myocardial infarction than were those who took naproxen 1000 mg.[2] Furthermore, findings of subsequent observational studies[3,4] of naproxen 1000 mg have not shown a protective effect sufficient to explain this difference. Therefore, adverse cardiovascular events could be a side-effect of the selective inhibitor of cyclo-oxygenase 2 (COX-2) and non-steroidal anti-inflammatory drug (NSAID) rofecoxib. Our aim was to compare risk of acute myocardial infarction (AMI) and fatal coronary heart disease (CHD) in users of rofexocib, with risk in users of other frequently prescribed NSAIDs in the expanded Tennessee Medicaid programme, TennCare. Our study included an a priori analysis of rofecoxib at doses greater than 25 mg because such doses, not presently recommended for long-term (>5 days) use,[5] could be uniquely associated with adverse cardiovascular effects.[1,5]

Cohort – Example (con't)

Cohort entry and cohort exit

We included individuals in the cohort from the first study day of current use, and stopped follow-up at the end of study eligibility, after 365 days of no NSAID use, or at time of switching from one NSAID to another.

Classification of exposure

We classified every person-day of cohort membership, according to NSAID use, as current (date prescription filled through end of days' supply), former (use during past 365 days), or non-use.

Analysis

We estimated adjusted incidence rate ratios (IRR) for NSAID exposure groups from a Poisson regression model.

Cohort - Example (con't)

	Non-user (n=202 916)	Ibuprofen (n=59 007)	Naproxen (n=70 384)	Celecoxib (n=22 337)	Rofecoxib ≤25 mg (n=20 245)	Rofecoxib >25 mg (n=3887)
Age (mean, SD) (years)	61·8 (9·0)	60·4 (8·1)	60·4 (8·1)	63·7 (8·9)	63·2 (8·8)	60·6 (8·1)
Women	127 458 (63%)	40 661 (69%)	48 592 (69%)	16 280 (73%)	14 830 (73%)	2552 (66%)
White	151 568 (75%)	40 065 (68%)	49 626 (71%)	16 246 (73%)	15 561 (77%)	2998 (77%)
TennCare enrolment, uninsured†	74 718 (37%)	18 247 (31%)	23 054 (33%)	5780 (26%)	5884 (29%)	1184 (31%)
Treatment for cardiovascular problems in past year‡	155 681 (77%)	49 684 (84%)	58 864 (84%)	19 778 (89%)	17 618 (87%)	3350 (86%)
Major cardiovascular disease§	69 150 (34%)	23 213 (39%)	27 011 (38%)	9625 (43%)	8507 (42%)	1640 (42%)
Cardiovascular drug¶	150 846 (74%)	48 183 (82%)	57 186 (81%)	19375 (87%)	17 243 (85%)	3256 (84%)

	Person-years	Events	Rate/1000	Adjusted IRR (95% CI)
Non-user	237 975	3085	13·0	1·00
New user during study				
Ibuprofen	4319	52	12·0	1·01 (0·77–1·33)
Naproxen	6489	72	11·1	0·92 (0·73–1·16)
Celecoxib	4509	55	12·2	0·88 (0·67–1·16)
Rofecoxib ≤25 mg	3430	47	13·7	1·02 (0·76–1·37)
Rofecoxib >25 mg	500	12	24·0	1·93 (1·09–3·43)

Case Control - Example

The New England Journal of Medicine

VOLUME 343 DECEMBER 21, 2000 NUMBER 25

PHENYLPROPANOLAMINE AND THE RISK OF HEMORRHAGIC STROKE

WALTER N. KERNAN, M.D., CATHERINE M. VISCOLI, PH.D., LAWRENCE M. BRASS, M.D., JOSEPH P. BRODERICK, M.D., THOMAS BROTT, M.D., EDWARD FELDMANN, M.D., LEWIS B. MORGENSTERN, M.D., JANET LEE WILTERDINK, M.D., AND RALPH I. HORWITZ, M.D.

ABSTRACT

Background Phenylpropanolamine is commonly found in appetite suppressants and cough or cold remedies. Case reports have linked the use of products containing phenylpropanolamine to hemorrhagic stroke, often after the first use of these products. To study the association, we designed a case–control study.

Methods Men and women 18 to 49 years of age were recruited from 43 U.S. hospitals. Eligibility criteria included the occurrence of a subarachnoid or intracerebral hemorrhage within 30 days before enrollment and the absence of a previously diagnosed brain lesion. Random-digit dialing identified two matched control subjects per patient.

PHENYLPROPANOLAMINE is a synthetic sympathomimetic amine commonly found in appetite suppressants and cough and cold remedies. Each month, millions of Americans use products containing phenylpropanolamine. Since 1979, more than 30 case reports have been published that describe the occurrence of intracranial hemorrhage after the ingestion of phenylpropanolamine.[1-9] Affected patients were most commonly adolescent girls or young women between the ages of 17 and 45 years who were using phenylpropanolamine-containing appetite suppressants, often for the first time.[7-18] In addition to the published reports, between 1969 and 1991, the Food and Drug Administration (FDA) re-

Results: "There were 702 patients and 1376 control subjects. For women, the adjusted odds ratio was 16.58 (95 percent confidence interval, 1.51 to 182.21; P=0.02) for the association between the use of appetite suppressants containing phenylpropanolamine and the risk of a hemorrhagic stroke …"

Conclusions

- Pharmacoepidemiology joins clinical pharmacology and epidemiology
- Pharmacoepidemiology plays an important role in Pharmacovigilance
- Significant increase in external activities and initiatives
- Number of observational research challenges to address for appropriate decision making
- Significant advances in the field are expected in the mid-term to long-term future

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Acknowledgment

Arnold Chan, MD, ScD, FISPE

Don Therasse, MD

Frank Andersohn, MD, PhD

Val Simmons, MB, BS, FFPM

Ken Hornbuckle, DVM, PhD

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Questions

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Back Up Slides

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Pharmacoepidemiological Questions

1) Are there differences in the number of people with hypertension diagnosed and treated among different populations in a given geographic area?
2) What is the effectiveness of psychotropic drugs in defined populations?
3) What factors in the physician-patient encounter influence treatment compliance and continuity of care?
4) How does cancer chemotherapy interact with the natural course of disease?
5) Is end-stage renal disease caused by regular analgesic use?
6) How can we accelerate the process of discovery of new, clinically relevant, intended, and unintended drug effects?
7) How clinically relevant is it to compare the effectiveness of an angiotensin-converting enzyme inhibitor with methyldopa for the treatment of mild hypertension?
8) What is the most appropriate control group for a hospital-based case-control study of drug-related congenital malformations?
9) Can we learn something about the prognostic factors for juvenile arthritis from the way it is treated by primary care physicians?

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Observational Research - Guidances

– **AHRQ REGISTRIES HANDBOOK**: Gliklich RE, Dreyer NA, eds. : Registries for Evaluating Patient Outcomes: A User's Guide. Prepared by Outcome DEcIDE Center. AHRQ Publ. No. 07-EHC001-1. Rockville, MD. 2007. 2nd edition, 2010

– **ENcEPP** Code of Conduct, Methods Guide, 2010. www.encepp.eu

– **GPP**: Guidelines for good pharmacoepidemiology practices Pharmacoepidemiology & Drug Safety 2008:17:200-208

– **GRACE** principles for observational studies of comparative effectiveness. Am J Man Care 2010;16(6):21-24

– **ISPOR Good Research Practices** for CER I, II, III . Value in Health 2009;1044-1072

– **STROBE**: Strengthening the Reporting of Observational Studies in Epidemiology, Epidemiology 2007;18(6): 805-835

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