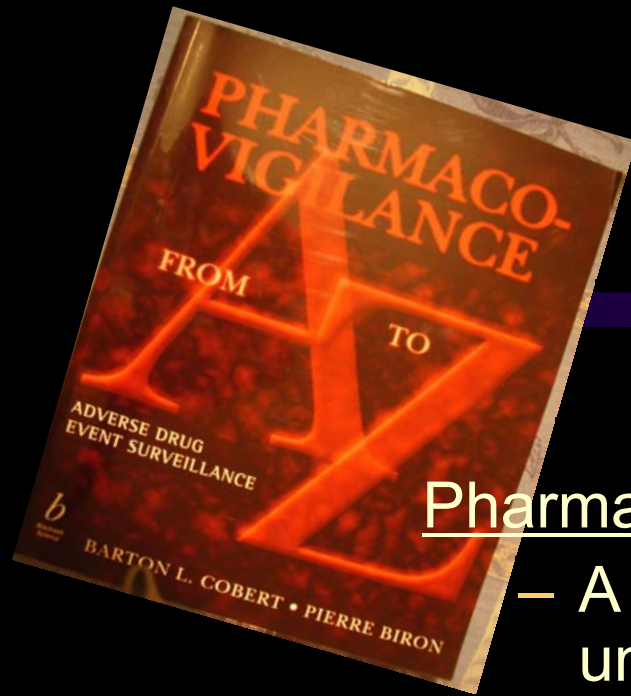


Pharmacoepidemiology

C. Ineke Neutel, PhD, FACE, FISPE

Definitions



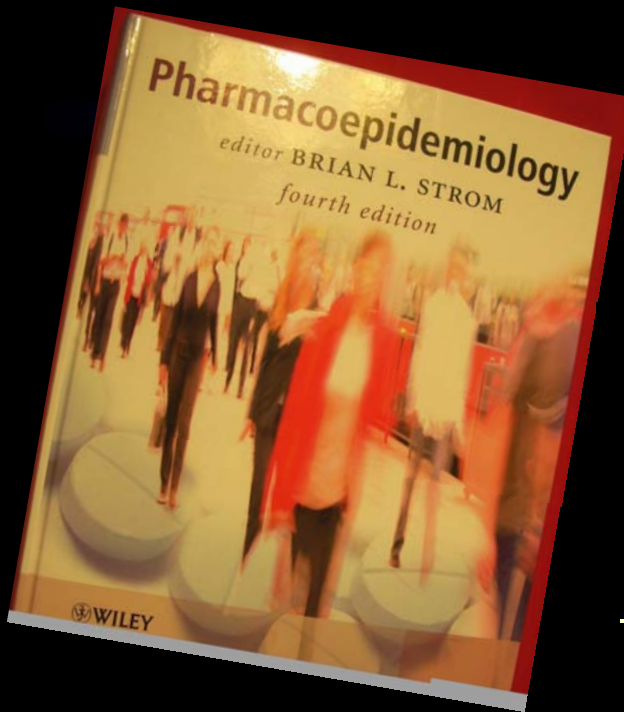
Pharmacovigilance:

- A clinical science using surveillance of undesirable effects of pharmaceutical products based on spontaneous reporting. (abbreviated from: Cobert & Biron, 2002)

Pharmacoepidemiology:

- “A medical science applied to the interaction between marketed medications and the population.” (Coberts & Biron, 2002)

Definition



Pharmacoepidemiology:

- Applying epidemiological methods to clinical pharmacology issues. (Strom, 2005)

Pharmacoepidemiology versus Pharmacovigilance

Pharmacovigilance:

- Largely hypothesis-generation
 - Signal generation
- Largely individual report oriented
 - ‘Causality’ within each report
 - Line listings
- In fact, a series of case-histories
 - No numerator, no denominator: no rates

Pharmacoepidemiology:

- Hypothesis-testing & hypothesis-generating
- Population oriented
- Causality as per Bradford-Hill criteria

Objectives



Workshop objective

- To understand the sources of data and risk assessment tools currently available to assess the safety of marketed health products.

Presentation objective

- To take a quick look at types of data sources used for pharmacoepidemiology
 - using an example

Example: Cox-2 Inhibitors



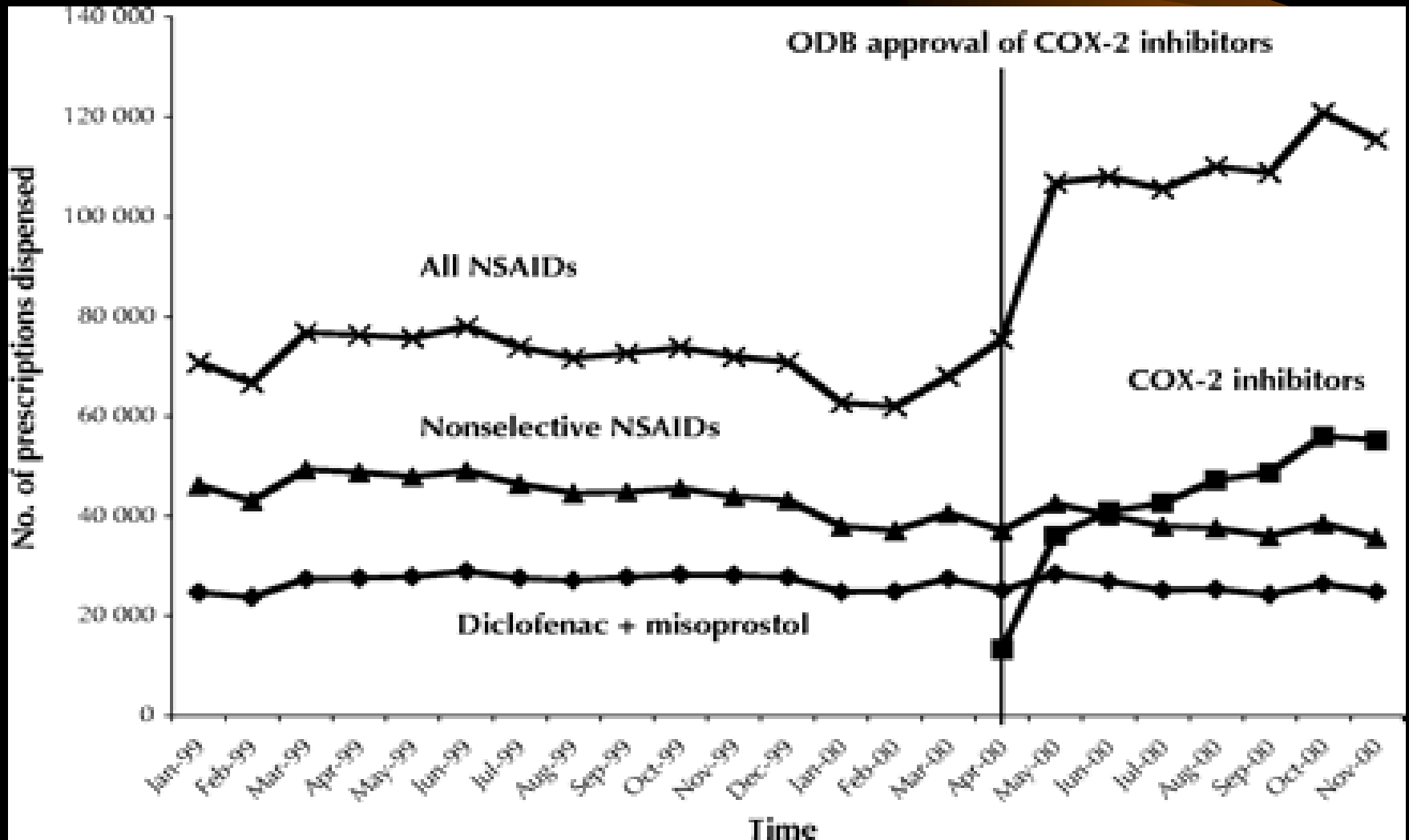
Celebrex eagerly anticipated

- TORONTO, ON - April 15, 1999. Health Canada approved Celebrex (celecoxib) . . . having received priority review . . .
- Since introduction in the US, Jan. 1999, Celebrex has become one of the fastest selling new drugs in history.

Why the anticipation?

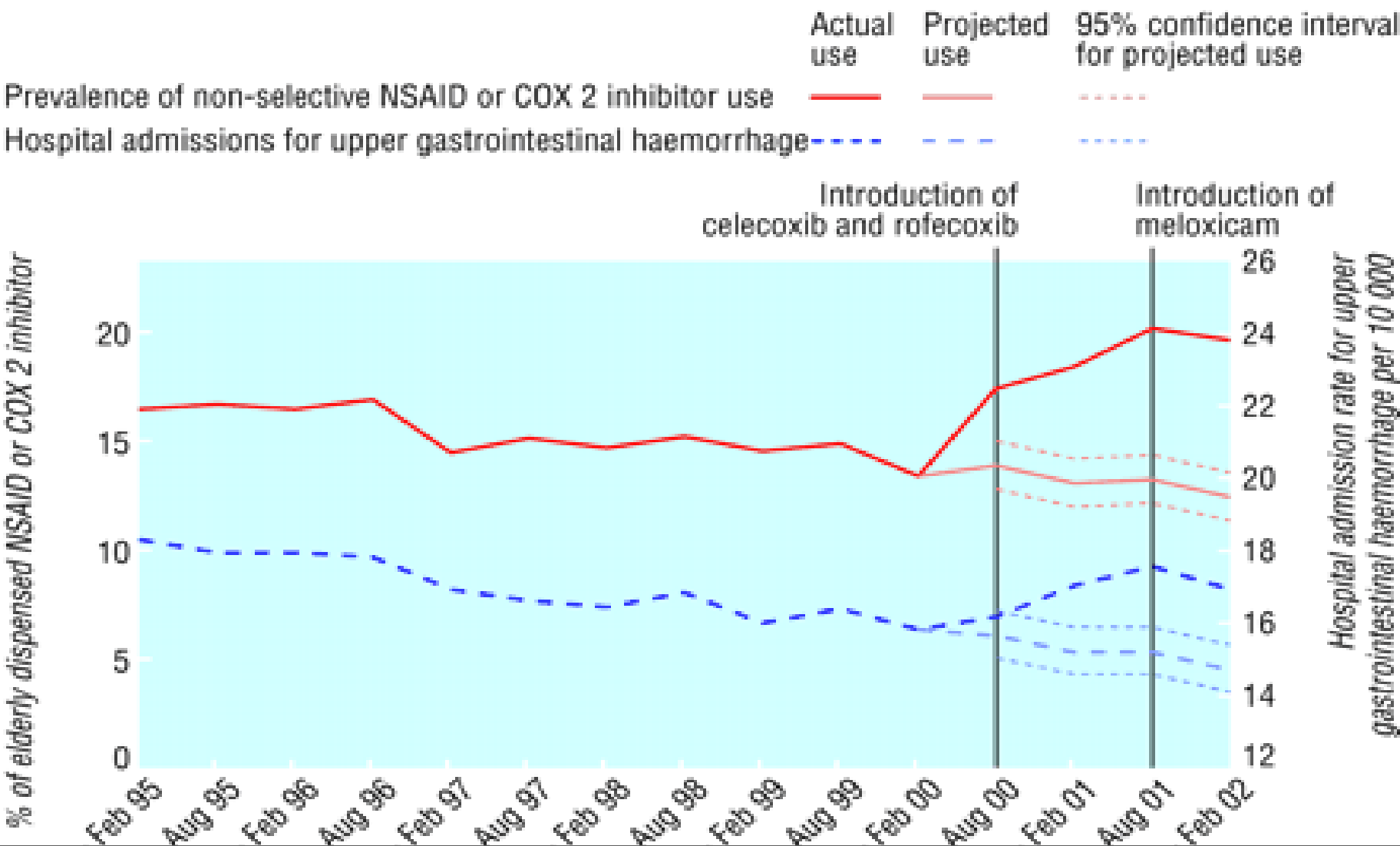
- Traditional NSAIDs
 - Inhibit both COX-1 and COX-2 enzymes. ,
 - Desired effect: relieving pain and inflammation
 - Undesired effect: damage to the stomach lining
 - Intestinal ulcers, GI bleeds
- Celebrex
 - Blocks COX-2 enzyme
 - which reduces pain and inflammation
 - Without blocking the COX-1 enzyme
 - which protects the gastrointestinal system.

NSAID use after COX-2 Inhibitor introduction



Reference: Mamdani M, et al. Initial patterns of use of COX-2 inhibitors by elderly patients in Ontario: findings and implications. CMAJ 2002; 1125-6.

Cox-2 inhibitors and GI Bleeds



Reference: Mamdani M et al, Gastrointestinal bleeding after the introduction of Cox 2 inhibitors: ecological study. BMJ 2004; 328:1415-6

Who is getting the Cox-2 inhibitors?

Moride et al, U. Montreal

- Data: Quebec Health Care Databases,
 - RAMQ Quebec Drug Plan; Hospital data
- Cox-2 inhibitors show increased use by:
 - The elderly, women
 - High risk patients:
 - high dose
 - anticoagulants
 - prior gastropathy, prior gastroprotective agents
 - other comorbidity
 - **first-time users
- Conclusion: channelling to high risk groups

Reference: Moride Y et al: Prescription channelling of COX-2 inhibitors and traditional nonselective nonsteroidal anti-inflammatory drugs: a population-based case-control study. *Arthritis Res Ther* 2005; 7:R333-42



**Bomb
Shell**

Not only still GI bleeds but also
Increased risk of CVD morbidity

COX-2 Inhibitors: CVD risk from existing studies

- Pre- and post-approval RCT, meta-analysis
- Existing clinical trials with different objectives:
 1. measuring GI effects
 2. examining protective effect for persons with history colorectal polyps.
 3. examining protective effect for Alzheimer's Disease


COX-2 inhibitors and CVD risk

Investigator: David Graham, FDA

- To examine increase in risk of CHD by Vioxx or naproxen
- Data: Kaiser-Permanente Managed Care Organization
- Study population:
 - Patients on COX-2 inhibitors or other NSAIDs
 - No CV, renal, etc. in previous 12 months
 - Followed to AMI event, death or end of study
- Matched controls, four for each case
- Outcome:
 - Rofecoxib increases risk of serious CHD, esp. high dose;
 - No protective effect of naproxen

Reference: Graham DJ et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclooxygenase 2-selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet* 2005; 365:475-481

Canadian Expert Advisory Panel on the Safety of Cox-2 NSAIDs (June, 2005)



Questions:

1. Do Celebrex, Bextra, Vioxx increase risk of CV events?
2. What is role of low-dose aspirin in patients on Cox-2 inhibitors?
3. Do overall benefits of Celebrex, Bextra and Vioxx justify marketing the drugs in Canada?
4. Are there patient populations in which potential benefits outweigh potential risks?
5. What actions does panel recommend?
6. What further research is essential to further evaluate potential CV risk of all NSAIDs?

Research recommended by panel



1. Further analyses of existing data
2. Future clinical trials
 - Sufficient power to identify small but clinically important increases in CV events as well as GI events
 - Effect of additional low dose ASA
3. Post-marketing evaluation
 - Utilization of outcomes in ‘real world’
 - Rare side effects
 - No exclusion of high risk patients.
4. Adverse event reporting
 - Rare and unusual events
 - Less useful for assessing CV risk

Drug data sources

- Provincial:
 - Ontario Drug Benefit ** and Quebec Drug Plan**
 - Others: Sask, BC, Manitoba
- National Drug data in European countries
- General Practice networks
 - HMO: Kaiser-Permanente
 - GPDR in UK
- Institutions
 - Hospitals, LTC
- IMS: Pharmacy retail: Rx** or total drug sales
 - Others: wholesale. CDTI
- Others:
 - National Population Health Surveys:
 - **NPHS (longitudinal), CCHS**
 - Insurance data