Pharmacoepidemiological Studies

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Pharmacoepidemiology Definition

Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people.

Strom B.L. 1989

Major Objectives of Pharmacoepidemiology

- to measure population - based benefits and risks of drug use
- to assess the benefit - risk ratio
- to analyse the prescribing of drugs and its determining factors
- to analyse the people's actual use of drugs and its determinants
- to implement pharmaco-epidemiologic knowledge into action
- to evaluate the former
- to describe and analyse the economics of drug use
- to advise decision-makers

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ICH Harmonised Tripartite Guideline E1

The Extent of Population Exposure to Assess Clinical Safety for Drug Intended for long term Treatment of Non-Life-Threatening Conditions

300 - 600	patients treated for six months at dosage levels intended for clinical use
100	patients exposed for a minimum of one year is considered to be acceptable

Randomized Trial

R:

Exposure	Diseased: yes	Diseased: no
yes	**a**	**b**
no	**c**	**d**

prospective

time

Relative Risk: $\frac{a}{(a + b)} : \frac{c}{(c + d)}$

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Large Randomized Trials with LEAN Protocol Characteristics

- ✓ single purpose-trial, no ancillary studies
- ✓ population-oriented eligibility criteria for patients, physicians and institutions
- ✓ measurement of relevant and reliable baseline, follow-up and outcome data only
- ✓ no collection of routine data
- ✓ no measurement of efficacy
- ✓ multicenter, centrally randomized
- ✓ blinded assessment of outcome criteria
- ✓ *Hasford J. Pharmacoepidemiol Drug Safety 3:321-327 (1994)*

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Assessment of the Safety of Pediatric Ibuprofen

Lesko S.M., Mitchel A.A.: JAMA 273:929-933 (1995)

OBJECTIVE to compare the risks of hospitalisation for GI-bleeding, renal failure or anaphylaxis among febrile children with Ibuprofen or Acetaminophen

DESIGN Randomized, double-blind trial Lean Protocol

SETTING Outpatient pediatric and family medicine practices

PATIENTS 84,192 Children

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Assessment of the Safety of Pediatric Ibuprofen

Lesko S.M., Mitchel A.A.: JAMA 273:929-933 (1995)

OUTCOME ASSESSMENT

Mailed SAQ or telephone follow-up four weeks after enrollment (18 questions)

- Nature of febrile illness
- Amount of study medication taken
- Supplement treatment
- Occurrence of any serious medical events
- Hospitalisations
- Hospital records

DURATION

28 months

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Contraindications

the same as for all prospective methods, except MRL

- Low Incidence of Adverse Events
- Long Latency Period
- Cumbersome and Risky Diagnostic Techniques

Cohort Study

Exposed	Diseased: yes	Diseased: no
yes	**a**	**b**
no	**c**	**d**

prospective

time

Relative Risk: $\frac{a}{(a + b)} : \frac{c}{(c + d)}$

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Cohort Study - Relative Risk

Cardiovascular Death

OCs	Present	Absent	Total
Ever Users	10 (a)	(b) 9538	9548
Never Users	3 (c)	(d) 7494	7494
Total	13	17032	N = 17045

$$\text{Relative Risk} = \frac{10 / (10+9538)}{3 / (3+7494)} = \frac{0.0010473}{0.0004001} = \mathbf{2.62}$$

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Cohort Study - Attributable Risk

Cardiovascular Death

OCs	Present	Absent	Total
Ever Users	10 (a)	9538 (b)	9548
Never Users	3 (c)	7494 (d)	7494
Total	13	17032	N = 17045

Attributable Risk 0.0010473 - 0.0004001 = 0.0006472

Without OCs 6.472 cardiovascular deaths per 10,000 were saved

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Risk Measures

The **relative risk** indicates the increase or decrease of risk associated with exposure. The RR is independent of the denominator.

The **attributable risk** (excess risk) is the part of the rate of disease / AE in exposed individuals that can be attributed to the exposure.

The AR is essential in considering the public health impact.

Cohort Study

ADVANTAGES

- prospective approach (C ➲ E)
- relative risk directly computable
- assessment of multiple outcomes
- standardized observation
- transparent analysis
- monitoring of rarely used drugs

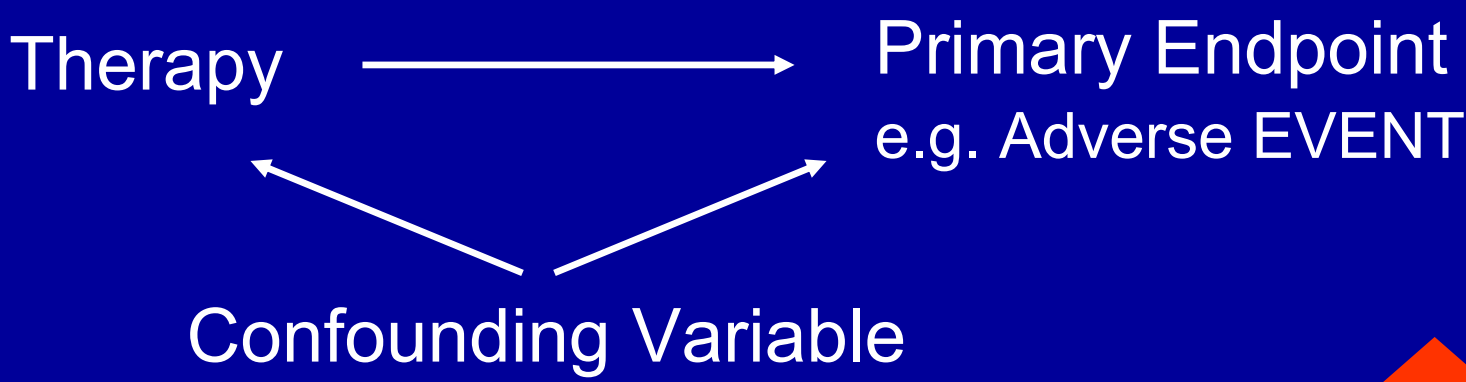
Cohort Study

PROBLEMS

- selection of the comparator group
- confounding by indication
- rare ADRs
- ADRs with long latency interval
- time consuming
- lost to follow-up participants
- logistic requirements and costs

”A confounding variable is an extraneous variable that, by virtue of its relationship to drug exposure and the clinical outcome under study, may artifactually create an apparent association or mask a real one”.

Strom B.L., Miettinen O.S., Melmon K.L.: Am J Med 77:703 (1984)



Gray-Donald K., Kramer M.: Am J Epidemiol 127:885 (1998)

COMPARISON Causality inference in observational vs. experimental studies

OBJECTIVE Impact of formula supplementation on duration of breast feeding

DESIGN Cohort-study vs. RCT

		Breast feeding at 9 weeks	
Supplemental feeding		Cohort Study	RCT
	YES	52%	55%
	NO	78%	54%

Case Control Study

Exposed yes	Exposed no	
a	b	yes cases
c	d	no Controls

Diseased

retrospective

time

$$\text{Odds Ratio} = \frac{ad}{bc}$$

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Case Control Study

- Cases and Controls should be identical except for the disease
- Cases and Controls should be representative for their population
- Cases and Controls should have had the same chance to get exposed.

Case Control Study

ADVANTAGES

- rare events
- long latency intervals
- fast and inexpensive
- no ethical problems
- many aetiological factors at the same time

PROBLEMS

- particularly prone to bias
  - selection of cases
  - selection of controls
  - exposure assessment → recall bias
  - confounding by indication
- Retrospective approach
  - causes ← effects
  - quality of historic data
- Relative risk and attributable risk not directly computable
- rarely used drugs

Selection Bias

- Cases or Controls are included by exposure
  - OC-users may be more intensively examined for VTE
- Cases and Controls stem from different populations, e.g. cases are outpatients, controls are inpatients.

Ascertainment or Recall Bias

- Cases and Controls recall differently drug exposures,
  e.g. mother of a child with congenital malformation
- Investigators are not blinded and may thus search for exposures depending to the case or control status

Confounding - Examples

- some -sympatomimetrics were prescribed for patients with more severe asthma
- the Osmogits / Ammogits and COX2-Inhibitors were thought to be safer and were prescribed to higher risk patients
- 3rd generation OC were prescribed to women at higher risk for VTE
- and thus more AE occurred

Causality Assessment in Observational Studies

No randomization ➲ no proof of causality

A Relative Risk or Odds Ratio ≠ 1 just indicates a potential association

- Exclude and / or assess bias
- Assess Causality using Bradford-Hill criteria
  - temporal sequence: cause ➲ effect
  - strength of the association
  - dose-response relationship
  - reversibility
  - consistency
  - biological plausibility
  - analogy

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Case-based Pharmacovigilance System

Screening Hospital Admissions and Estimating Incidences using Drug Consumption Data

Schneeweiss et al.: Eur J Clin Pharmacol 58:285-291 (2002)

Schneeweiss et al.: Br J Clin Pharmacol 52:196-200 (2001)

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Guiding Ideas

- Serious ADRs due to prescriptions to outpatients lead to Hospital Admission
- Systematic Screening of all non-elective Hospital Admissions should allow the identification of almost all serious ADRs of outpatient care ➲ Nominator
- The Assessment of Drug Usage in the Hospital Service Areas (➲ Denominator) should allow the Estimation of incidence.

Methodology

Identification of SAEs / SADRs

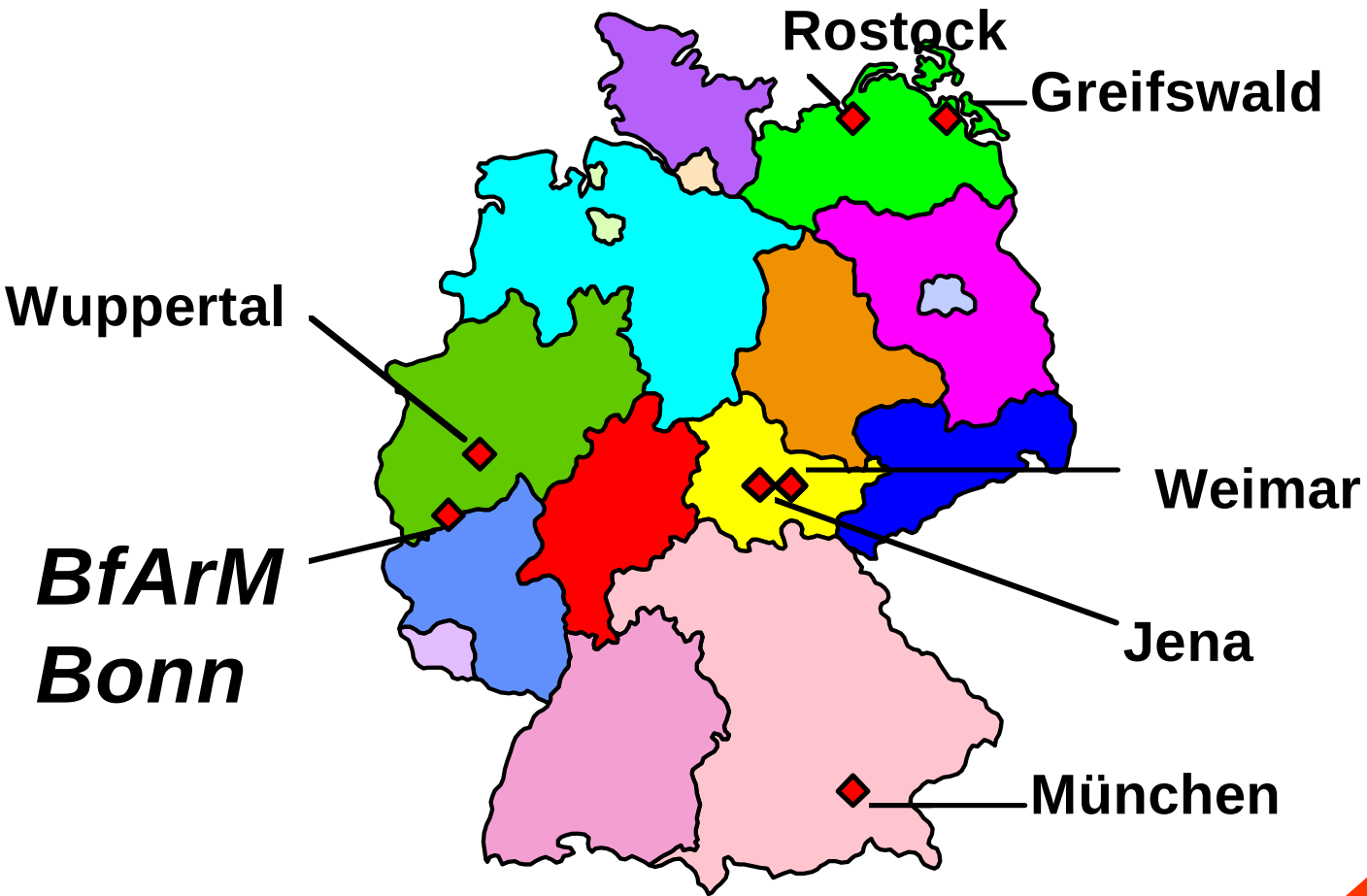
- Screening of all non-elective Hospital-Admissions using specified Screening Criteria, e.g.
  - Symptoms: GI-bleeding, Agranulocytosis
  - Patient characteristics, e.g. age > 60 yrs, impaired renal function
  - Drug Treatment, e.g. > 5 drugs administered
- Standardized Causality Assessment
  The 'French Way'

Design: Source population

- **Definition of Hospital Service Area:**
  - Sorted all hospital admissions by zip-code
  - All zip codes that cumulate 60% of admissions were included *(Wennberg et al.)*
  - Remaining 40% of admissions:
    - Spread over a wide area outside the urban centers
    - Patients were more likely to be admitted to regional hospitals.

Design: Exposure assessment

- **In source population:**
  - Drug dispensing information through Pharmacy Computing Centers for the 60 most prescribed drugs.
  - Treated patients per quarter = having at least 1 dispensing of a drug that quarter.
- **In cases:**
  - Detailed medication history by interview and chart review through clinical pharmacologist


Rostock
Greifswald
Wuppertal
Weimar
BfArM
Bonn
Jena
München

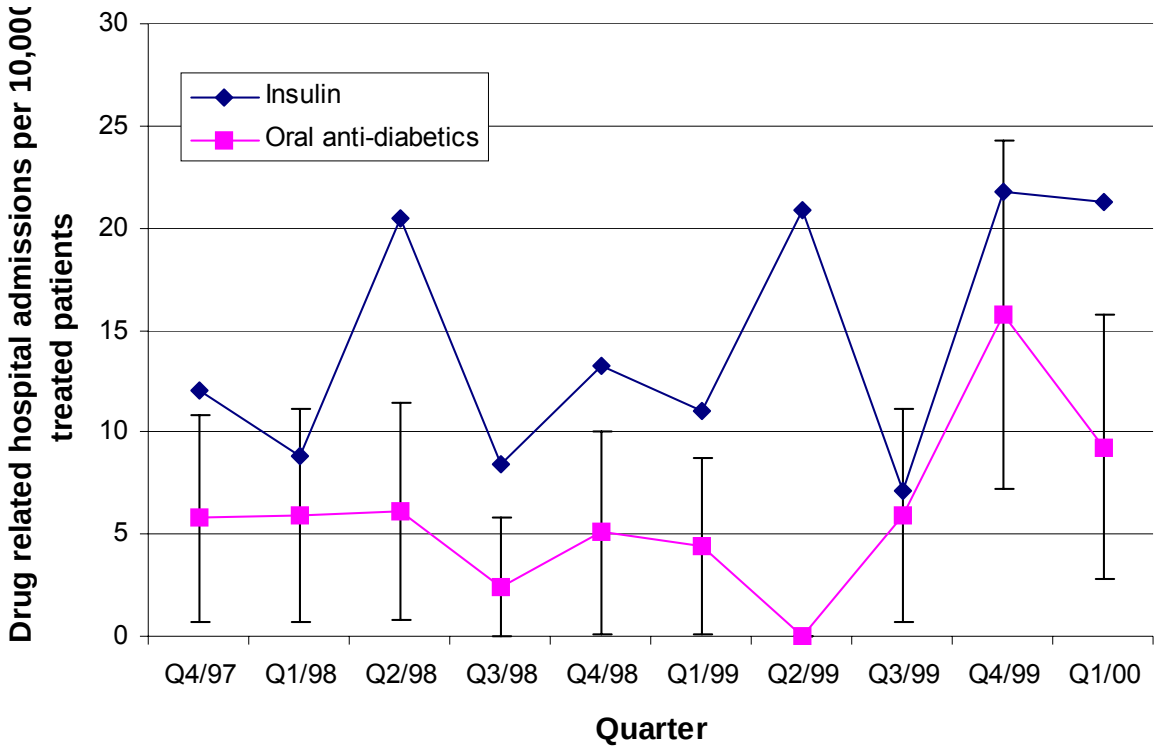
Involved Drug Groups

Anticoagulants (B01)	18%
Antiphlogistics /-rheumatics (M01)	11%
Antidiabetics (A10)	9%
Cardiac Drugs (C01)	9%
Analgesics (N02)	8%
ACE-Inhibitors (C09)	5%
Systemic Antibiotics (J01)	5%

Involved System / Organ Classes

GI-Tract	40%
Metabolism	11%
Generalized	11%
Cardiac Arrhythmias	8%
Hemostasis	5%
Liver & Gall	4%

Oral Antidiabetics and Insulin



Schneeweiss S, Hasford J, et al.: Hospital Admissions Caused by Adverse Drug Reactions: A Longitudinal Population-based Study. Submitted for publication

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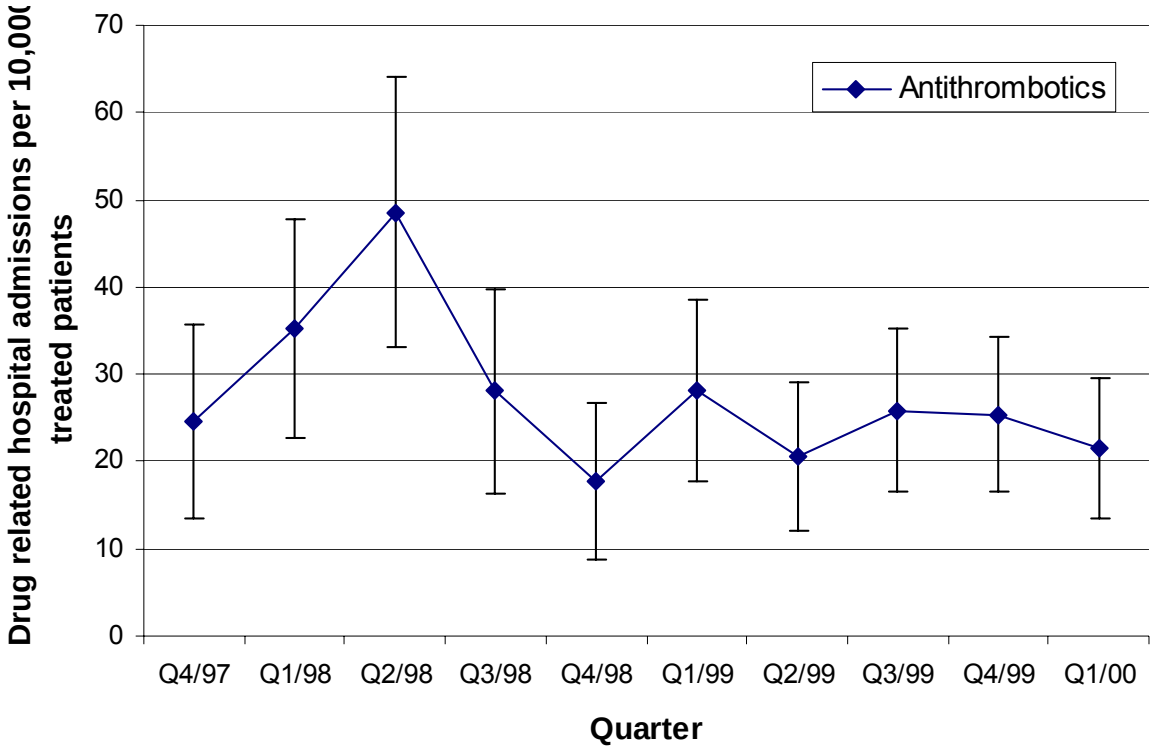
Antithrombotics



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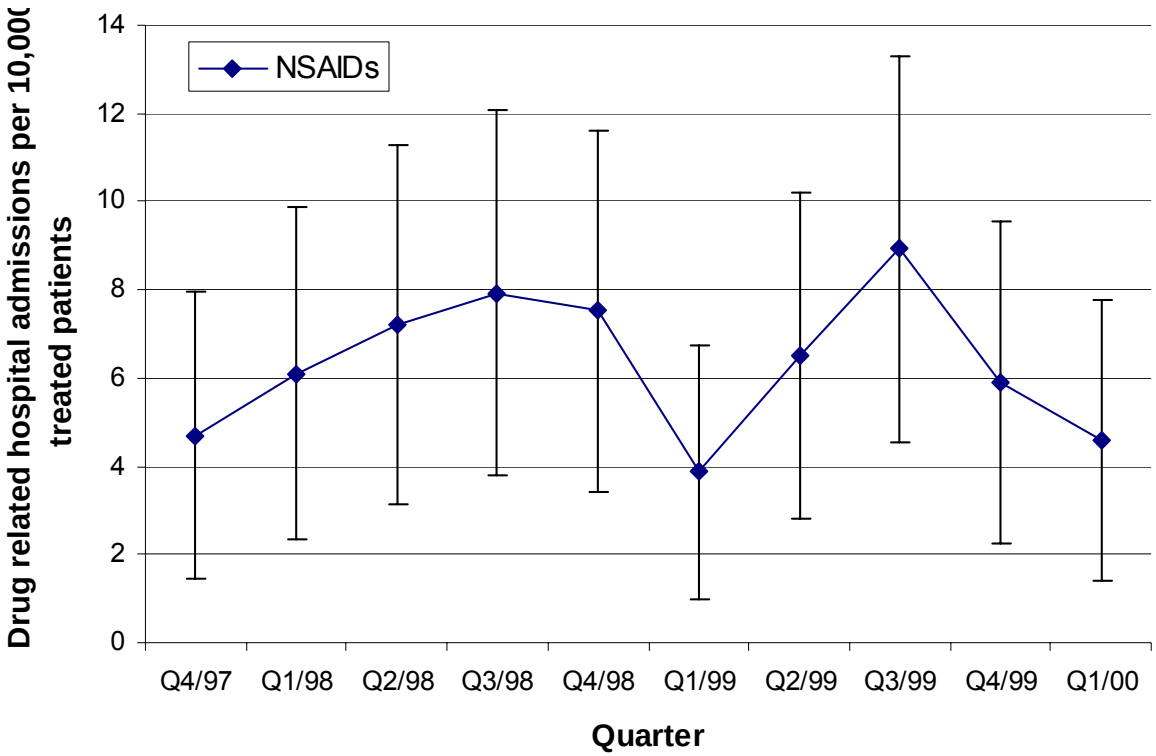
NSARs



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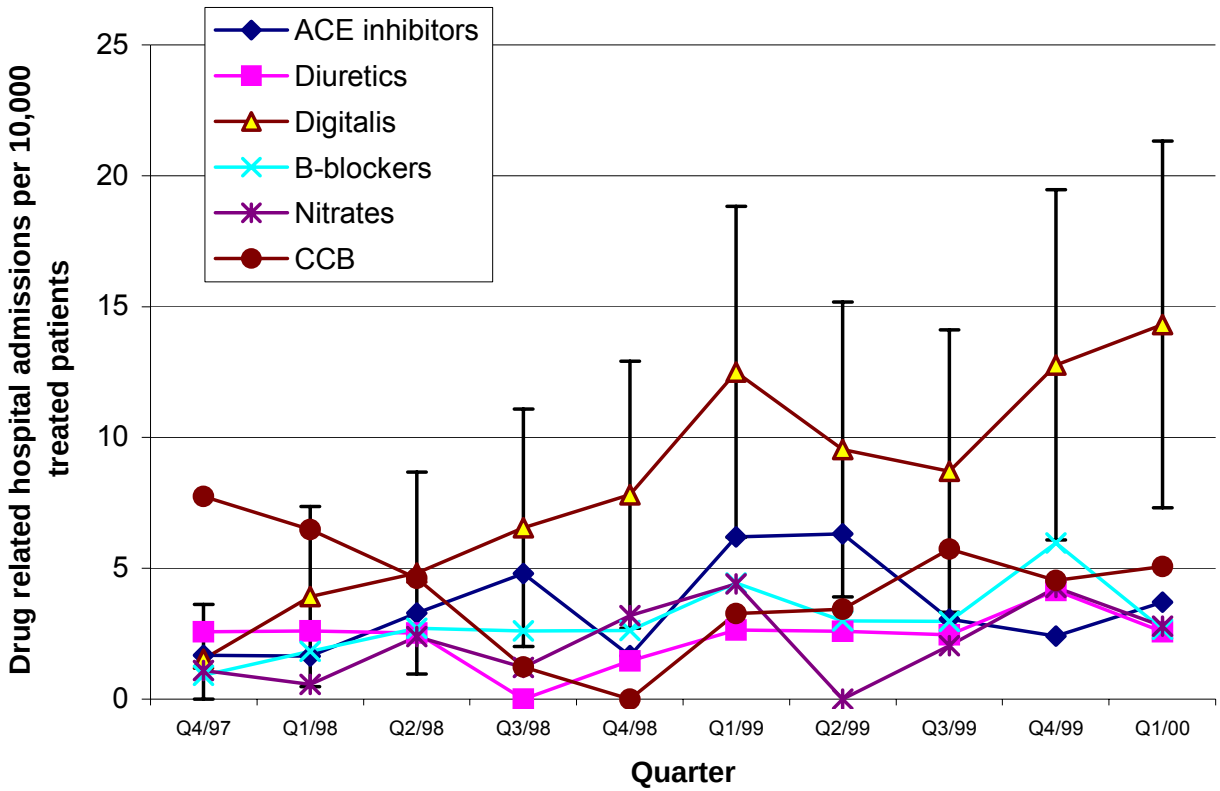
Cardiovascular Drugs



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Discussion

Nominator

Even careful Screening will not identify all SAEs and will thus result in some Underestimation of the true Incidence. This Bias is most probably stronger than the potential Bias due to false positive SADR causality Assessment.

Denominator

It is difficult to estimate absolutely precise the Hospital Service Area and the regionalized Drug Consumption.

Can adverse drug reactions be detected earlier?
A comparison of reports by patients and professionals

Toine C.G., Egberts, Maartje Smulders, Fred H.P., de Koning, Ronalt H.B., Meyboom, Hubert G.M., Leufkens

Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht

Institute for Pharmaceutical Sciences, Utrecht University, Netherlands

Pharmacovigilance Foundation LAREB, Tilburg, Netherlands

BMJ 313:530-531 (1996)

Involving Patients in AE / ADR-Reporting

METHODOLOGY

Since 1990 there is a toll free telephone counselling service for problems with the use of medicines available in the Netherlands.

Paroxetine

Time to first report of an unexpected AE / ADR

AE / ADR	Patients	Physicians
Frequency	21%	18%
Rigours	390 days	578 days
Bleeding disorders	396	1025
Hypertension	432	1192
Mydriasis	597	660
Taste disturbance	635	827
Apathy	943	1124
Flushing	967	1100
Menstruate disorders	971	1162
Rash	1002	1125

Egberts TCG et al. BMJ 1996;313:530

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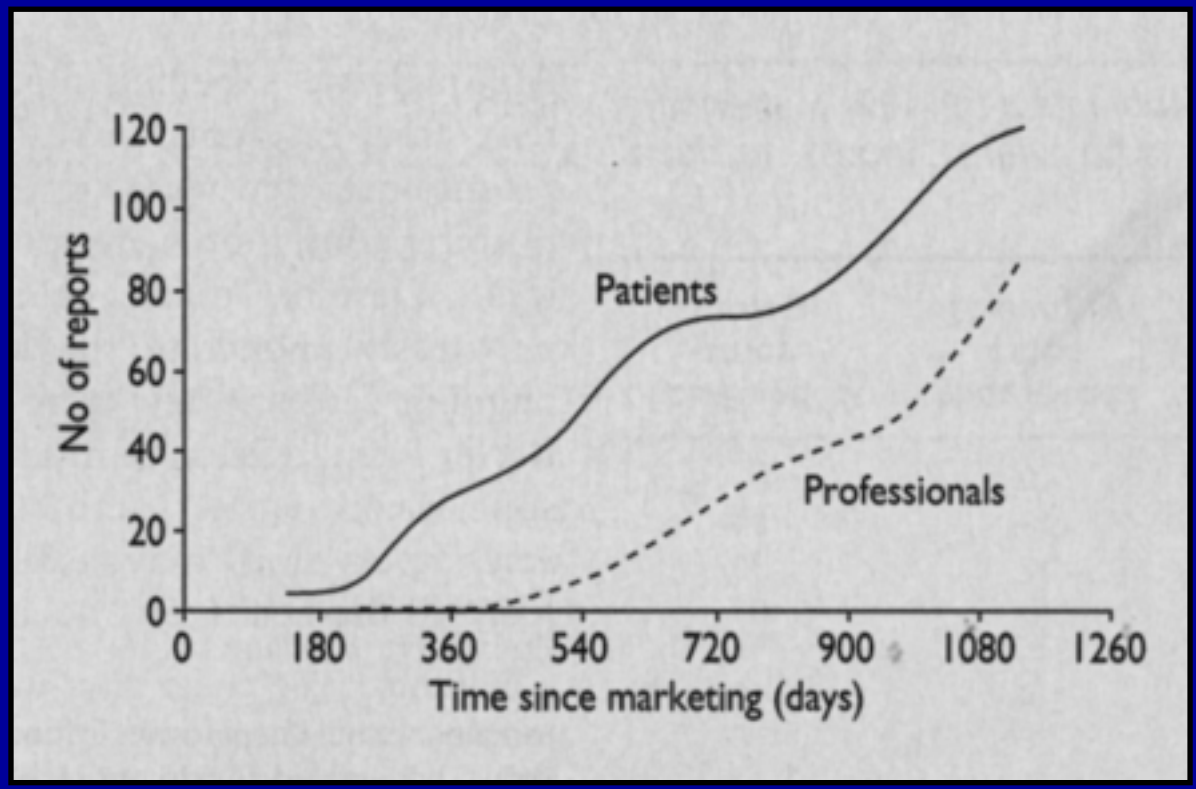
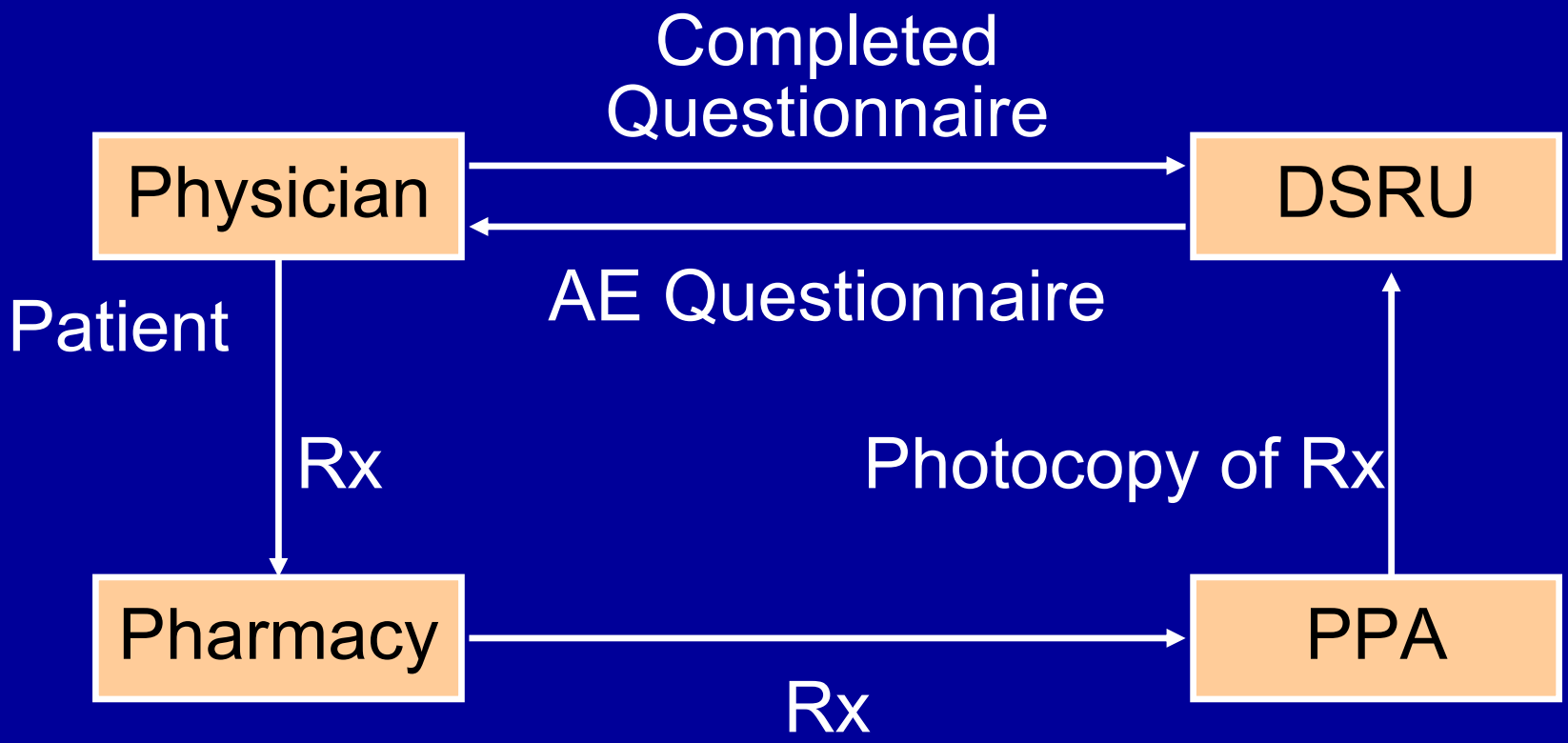


Fig. 1

Cumulative number of reports of suspected **adverse drug reactions** associated with use of paroxetine received from patients and from health care professionals since marketing (t=0).

Egbert et al. Can adverse drug reactions be detected earlier? A comparison of reports by patients and professionals. BMJ 1996;313:530-531

Prescription Event Monitoring



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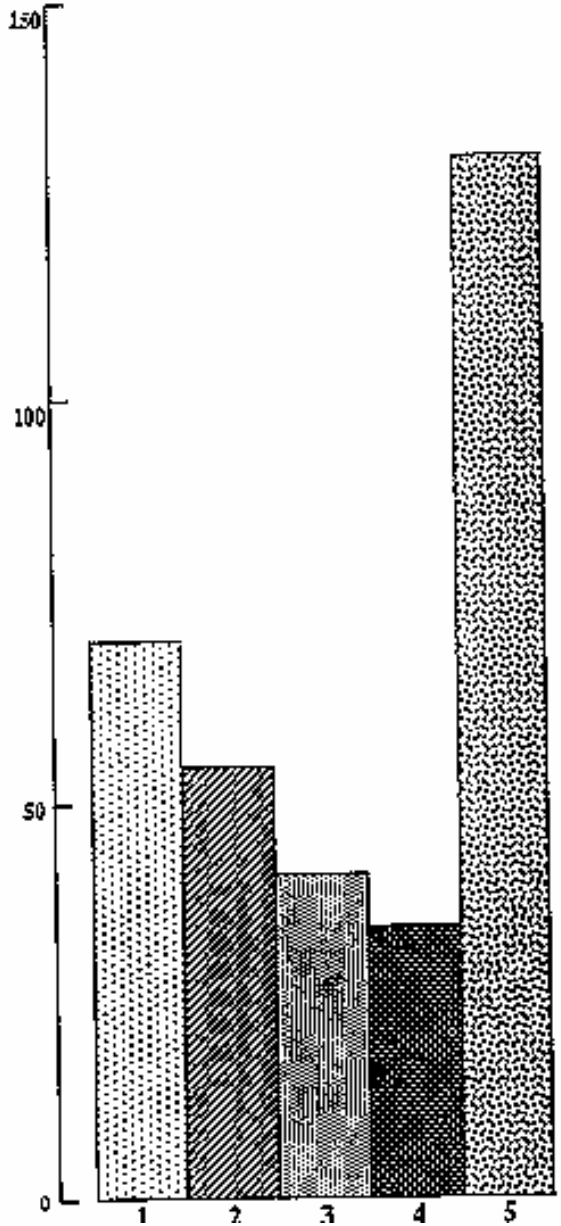
Advantages of PEM

- quick assembly of large cohorts (n ≈ 10,000)
- control groups
- access to medical records
- records events for up to six months after drug use

Problems of PEM

- response 55% - 70%
- readability ≈ 70%
- limited to up to five drugs at a given time
- outpatients only
- confounding by indication



1 Benaxaprofen
2 Fenbufen
3 Zomepirac
4 Piroxicam
5 Indomethacin (Osmosin)

Gastrointestinal events:

rate of events per 1000 Patient-Years of treatment

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” ’Osmosin’, a drug that was specifically promoted because the active ingredient was released slowly as the capsule passed down the alimentary canal thus, it was hoped, causing less irritation …

Whenever a new drug is promoted as a product which causes few side-effects, it is likely to be used in patients in whom such effects are more common. This may well be an important source of bias …”.

W.H.W. Inman 1986

Recent PEM-Studies

Cox2 Inhibitors

Glitazones

Sildenafil

Carvedilol

Raloxifene

Zarfirlukast

More Information: www.dsru.org

Medical Record Linkage

Method of assembling routinely collected person-related information contained in two or more records, e.g. in different sets of medical charts, in vital research such as birth and death certificates, in cancer registries or in sickness fund data bases.

- General Practitioner Research Data Base (www.mca.gov.uk/outwork/gprd/gprd.htm)
- Saskatchewan Health Care Data Base

MRL / Available Information

- ✓ personal identifier
- ✓ sex
- ✓ date of birth
- ✓ location
- ✓ diagnoses, out- and / or inpatient
- ✓ outpatient prescriptions
- ✓ dates
- ✓ other ressources used
- ✓ provider of service
- ✓ death certificates

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Cohorts of exposed persons

codein	1.68 Mio.
amoxicillin	1.41
penicillin	1.37
ibuprofen	0.48
miconazole	0.39
cefaclor	0.29
cimetidine	0.28
amitryptiline	0.21

Diagnoses

Otitis media	0.93	Mio.
Bronchitis	0.87	
Urinary tract infection	0.80	
Anaemia	0.62	
Dermatitis	0.52	
Hypertension	0.41	
Gastritis / Duodenitis	0.24	
Asthma	0.19	
Death	0.13	

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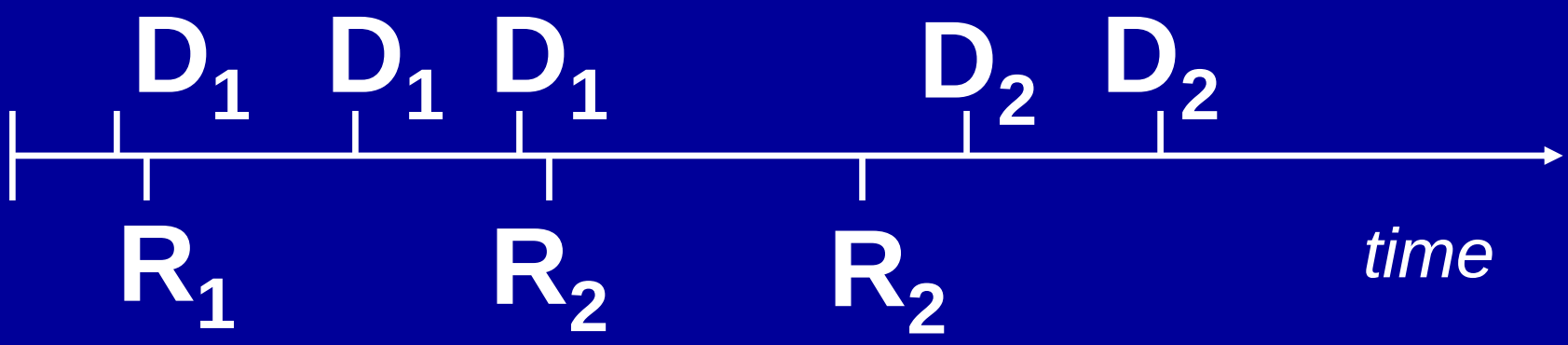

D = Diagnoses

R = Prescriptions

MRL / Pharmacoepidemological Data Bases

ADVANTAGES

- prospective data collection
- large sample sizes
- CS and CCR feasible
- incidence figures available
- outpatient and inpatient
- validity of the data
- quick results
- access to patients' records
- children, pregnant women

MRL / Pharmacoepidemological Data Bases

PROBLEMS

- rarely prescribed drugs
- very rare ADRs
- time lag of a couple of months
- variables like smoking, alcohol intake etc. missing
- validity of diagnoses?
- lost to follow-up
- legal problems, e.g. confidentiality issues

MRL - Analyses

NSAIDs	GI-bleeding
NSAIDs	allergies, anaphylactid reactions
Oral Contraceptives	gallbladder diseases, VTE
Thiazides	gallbladder diseases
Ampicillin	cutaneous reactions
Ticrynafen	liver diseases
Phenothiazines	liver diseases
Sulfonamides	thrombocytopenia
Procainamid	Cytopenia
KCl	GI-bleeding
β-Blocker	depression

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Conclusions

- There is no omnibus-design available.
- Specify the research question as detailed as possible and select the appropriate design which provides the highest validity.