The case-population strategy in pharmacovigilance

11th ENCePP Plenary Meeting

EMA, 18 June 2013

Joan-Ramon Laporte

Fundació Institut Català de Farmacologia

Three premises

Protect the patients

Early signals, prompt responses

Avoid unnecessary action

Robust and valid signals

Protect public health

Estimate the magnitude of risk and population impact

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New scenarios

ADRs 4th cause of death?

Need for a public health perspective

Increase in the risk of common diseases

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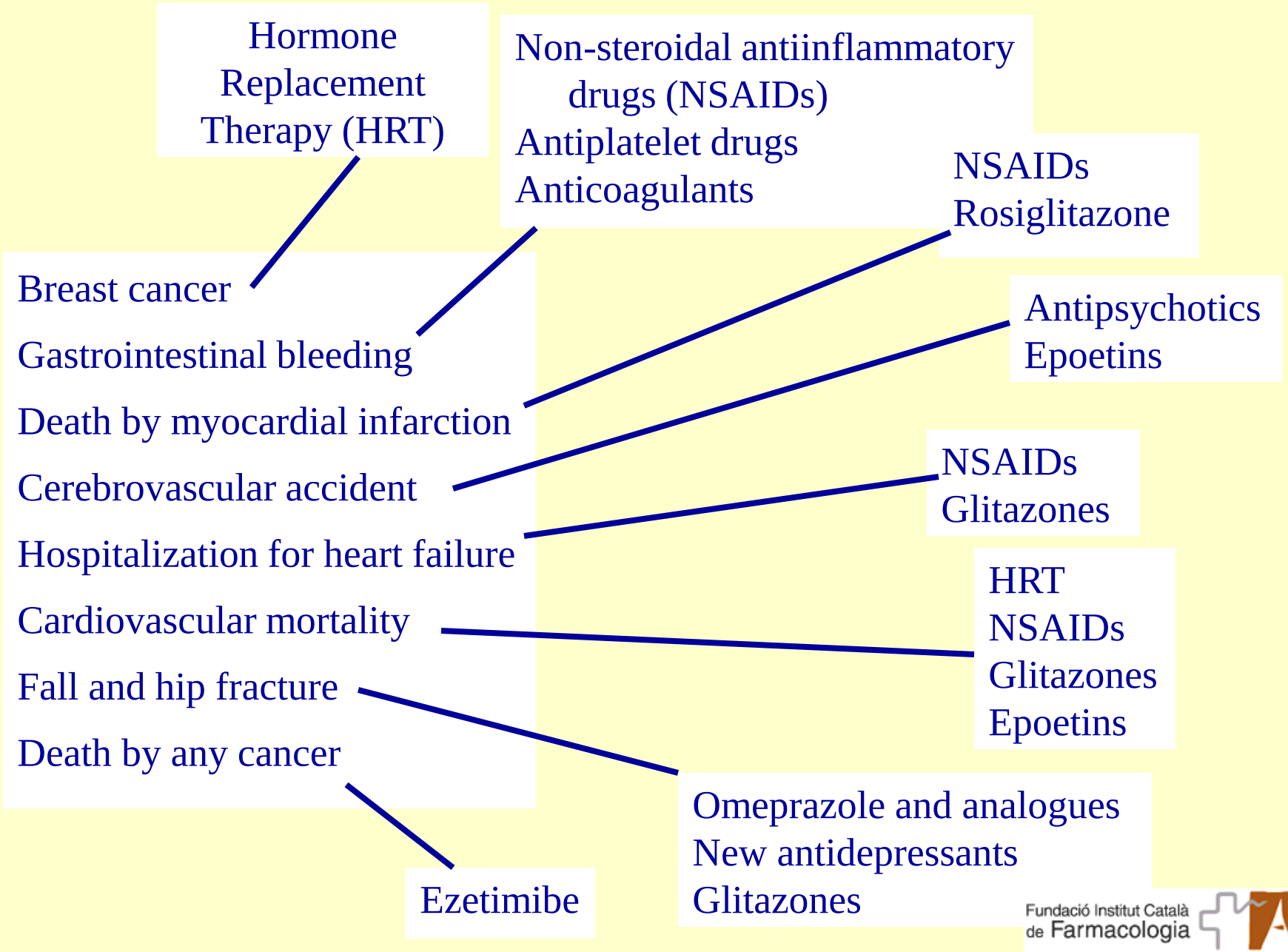
	Number of cases per million per year
Breast cancer	300
Gastrointestinal bleeding	400
Death by myocardial infarction	870
Cerebrovascular accident	2,300
Hospitalization for heart failure	2,200
Fall and hip fracture	800-1,800
Death by any cancer	1,730


Hormone Replacement Therapy (HRT)
Non-steroidal antiinflammatory drugs (NSAIDs)
Antiplatelet drugs
Anticoagulants
NSAIDs
Rosiglitazone
Antipsychotics
Epoetins
Breast cancer
Gastrointestinal bleeding
Death by myocardial infarction
Cerebrovascular accident
Hospitalization for heart failure
Cardiovascular mortality
Fall and hip fracture
Death by any cancer
NSAIDs
Glitazones
HRT
NSAIDs
Glitazones
Epoetins
Omeprazole and analogues
New antidepressants
Glitazones
Ezetimibe
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New scenarios

ADRs 4th cause of death?

Need for a public health perspective

Increase in the risk of common diseases

Higher public health impact of ADRs

Refinement of observational research

Meta-analysis of RCTs

Development and implementation of ICTs, registers, and EHRs

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Case-population in pharmacovigilance

→ Rationale

Examples

Conclusions

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Methods in pharmacovigilance

- Case reports
- Series of cases

Voluntary reporting

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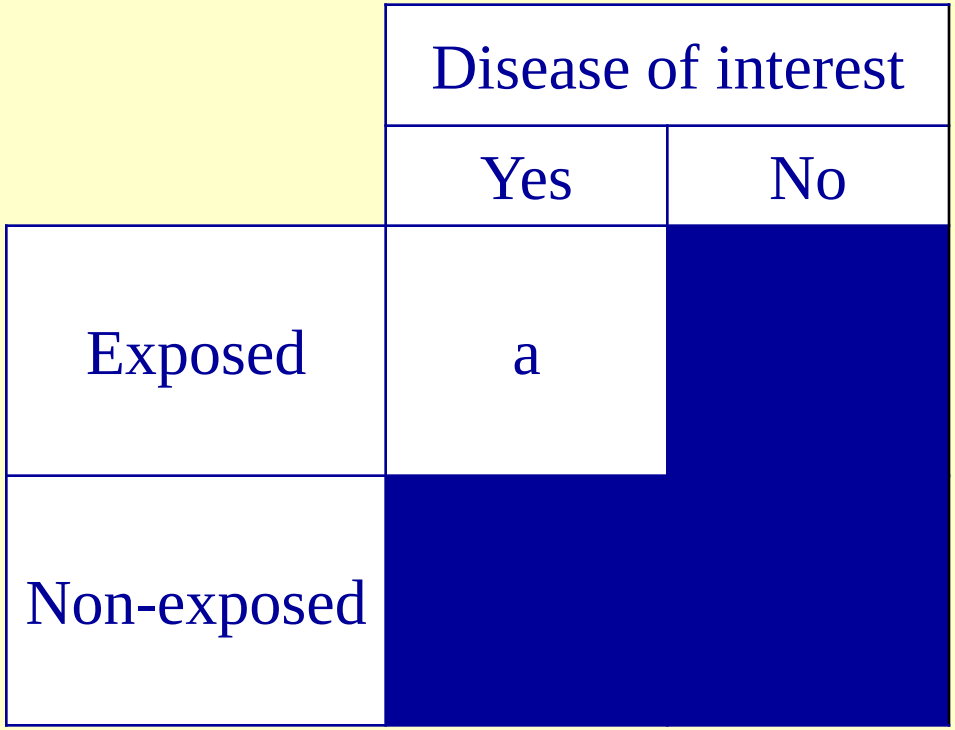
Voluntary reporting



Just a probably unrepresentative sample

Methods in pharmacovigilance

- Voluntary reporting

…

- Case-control studies
- Cohort studies
- (Meta-analysis of) RCTs

Anecdotal
No risk estimation
Clinical perspective
Natural history

Control group
Magnitude of association
Risk estimation
Epidemiological perspective

Incidence
Public health perspective

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Case-control study

	Disease of interest	
	Yes	No
Exposed	a	b
Non-exposed	c	d

Case-control study

	Disease of interest	
	Yes	No
Exposed	a	b
Non-exposed	c	d

$$OR = \frac{a \times b}{c \times d}$$

Case-control study

	Disease of interest	
	Yes	No
Exposed	a	b
Non-exposed	c	d

$$OR = \frac{a \times b}{c \times d}$$

Case-control study

- Prevalence of use = 1%
- $\alpha = 0.05$
- $\beta = 0.20$
- OR = 5
- 3 controls per case

200 cases

600 controls

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Case-control study

- Prevalence of use = 1‰
- $\alpha = 0.05$
- $\beta = 0.20$
- OR = 5
- 3 controls per case

2,000 cases

6,000 controls

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Case-control studies

Automated databases:

- Low numbers of cases of rare diseases
- Limited statistical power for subgroup analysis, dose-effect relationships, etc.
- May not be fully representative of the whole health system

Case-population study

- Define condition, set diagnostic criteria
- Ensure full ascertainment of cases, by a process which is independent of previous exposures or suspected causes
- Estimate the rate of exposure among the cases
- Estimate rate of exposure among the general population from consumption data
- Compare rates of exposure among cases with rates of exposure among general population

ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (10): 861-868
0114-5916/11/0010-0861/$49.95/0

The Case-Population Study Design
An Analysis of its Application in Pharmacovigilance

Hélène Théophile,[1,2,3] *Joan-Ramon Laporte*,[4] *Nicholas Moore*,[1,2,3] *Karin-Latry Martin*[1,2,3] and *Bernard Bégaud*[1,2,3]

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2 INSERM U657, Bordeaux, France
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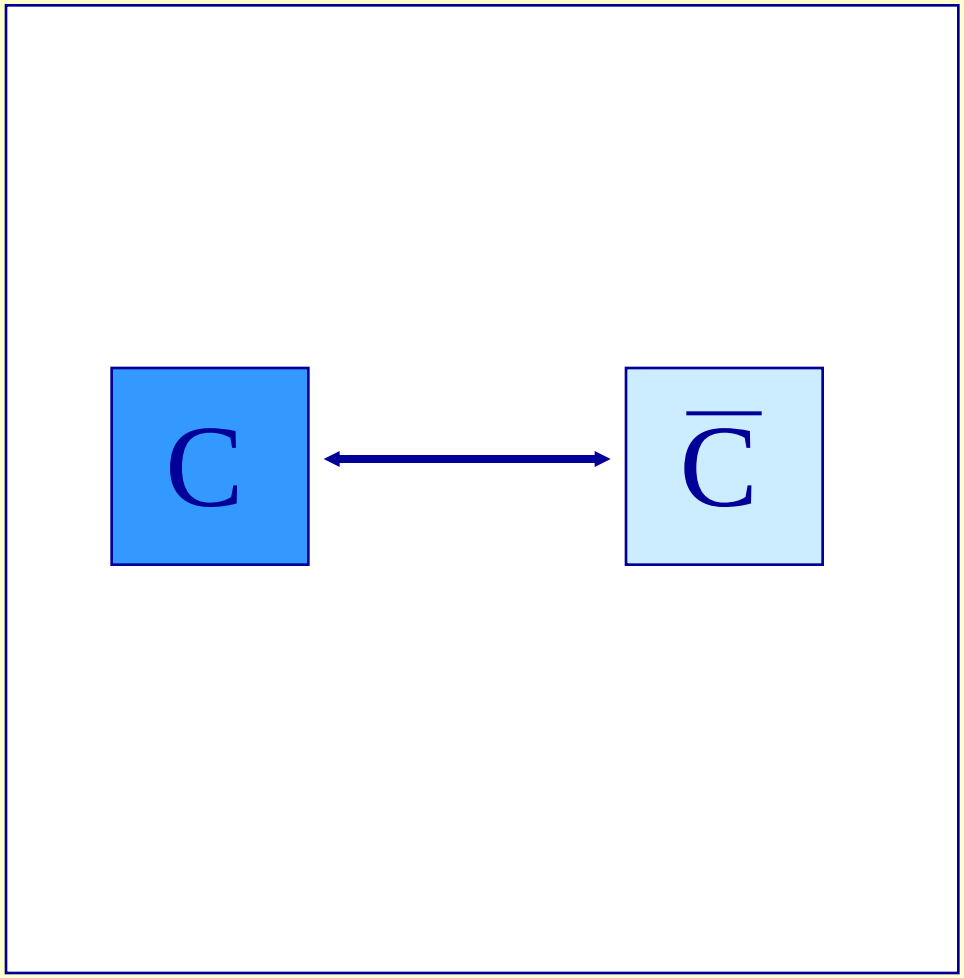
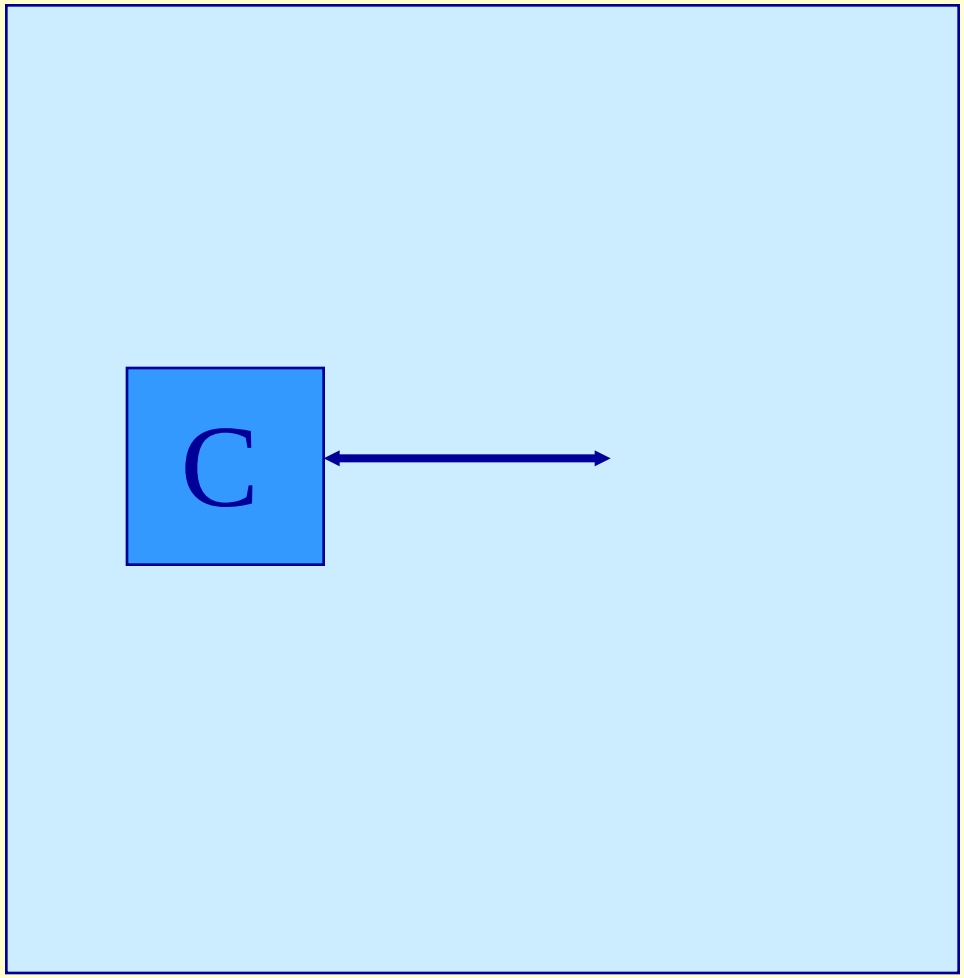
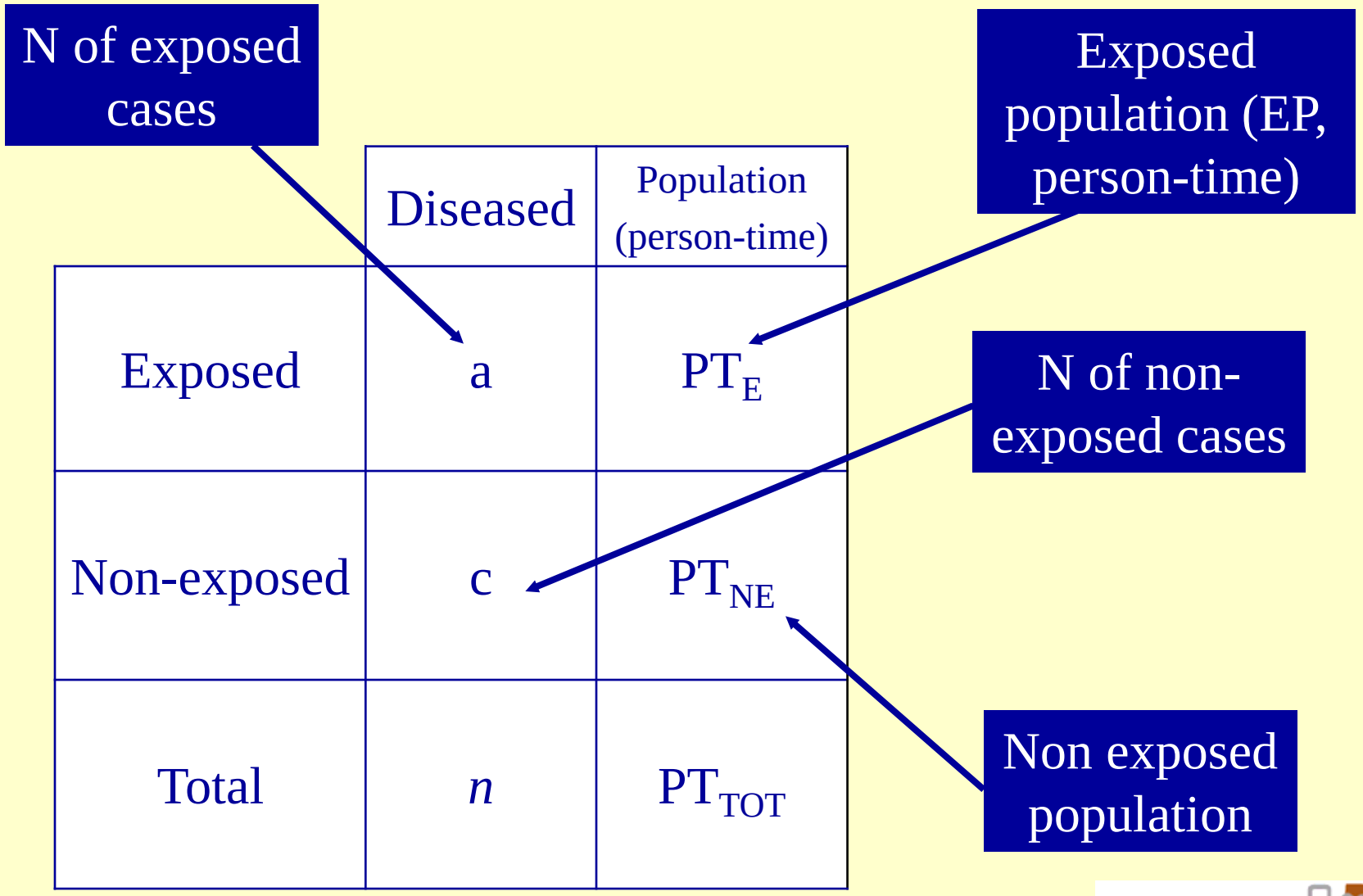
Case-control study



Case-population study





N of exposed cases

$$EP = \frac{\text{Consumption (mg)}}{\text{DDD (in mg)} \times 365 \text{ days}}$$

	Diseased	PT
Exposed	a	PT_E
Non-exposed	c	PT_{NE}
Total	*n*	PT_{TOT}

N of non-exposed cases

$PT_{TOT} - PT_E$

N of exposed cases

EP= Consumption (mg) / DDD (…) × 365 days

osed

Total	*n*	PT_{TOT}

Four pieces of information:

- Cases and their exposures
- Consumption (weight units)
- Mean daily dose (not necessarily the DDD)
- Mean duration of treatment course

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Case-population in pharmacovigilance

Rationale

→ Examples

Conclusions

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Epidemiology of adverse drug reactions to phenformin and metformin

TABLE III—*Numbers of adverse reactions to phenformin and metformin reported in Sweden during 1975-7 and relation to sales*

	Phenformin	Metformin	P
Sales (× 10⁶ DDDs)	7·37	7·50	
Adverse reactions:			
Reported	16	12	NS*
Probable and not excluded ..	14	7	NS*
Lactic acidosis:			
Reported	13	2	0·01†
Probable and not excluded ..	13	1	0·001†
Fatal reactions:			
Reported	6		0·02†
Probable and not excluded ..	6		0·02†

DDD = Defined daily dose. NS = Not significant.
*χ^2 test. †Binomial test.

Eur J Clin Pharmacol (1990) 38: 387–388

... OF ERYTHROMYCIN IS MOST ... TOXIC?

THE LANCET, MAY 14, 1988

European Heart Journal (1991) **12**, 639–641

Br J Clin Pharmacol 1998; 46: 181–184

... and aplastic anaemia—

Eur J Clin Pharmacol (2000) 55: 761–764

... associat...

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

L. Ibáñez · E. Ballarín · E. Pérez · X. Vidal
D. Capellà · J.-R. Laporte

Agranulocytosis induced by pyrithyl...

the a...

Joan-Ramon Laporte,
...t Català de Farmacologia, Univ...

Risk of acute liver injury associated with the use of drugs: a multicentre population survey

M. SABATÉ*, L. IBÁÑEZ*, E. PÉREZ*, X. VIDAL*, M. BUTI†, X. XIOL‡, A. MASS, C. GUARNER¶, M. FORNÉ**, R. SOLÀ††, J. CASTELLOTE‡, J. RIGAU‡‡ & J.-R. LAPORTE*

Aliment Pharmacol Ther **25**, 1401–1409 2007

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Type B adverse and other rare ADRs

	OR (95%CI)	
	Case-control	Case-population
Agranulocytosis		
Dobesilate	23.66 (7.5-74.2)	39.55 (18.0-77.5)
Pirythyldione	200.1 (22.6-∞)	109.6 (57.5-191.5)
TEN		
Co-trimoxazole	160, 102	44.4 (28.4-69.4)
Carbamazepine	12, 72	24.4 (10.9-55.0)
Phenobarbital	8.7; 16.0	21.9 (14.6-32.9)
Piroxicam	12	14.5 (8.3-25.4)
Allopurinol	14.5; 5.5	3.4 (1.6-7.1)
PPH		
Appetite suppressants	23.1 (6.9-77.7)	31 (16.2-59.2)

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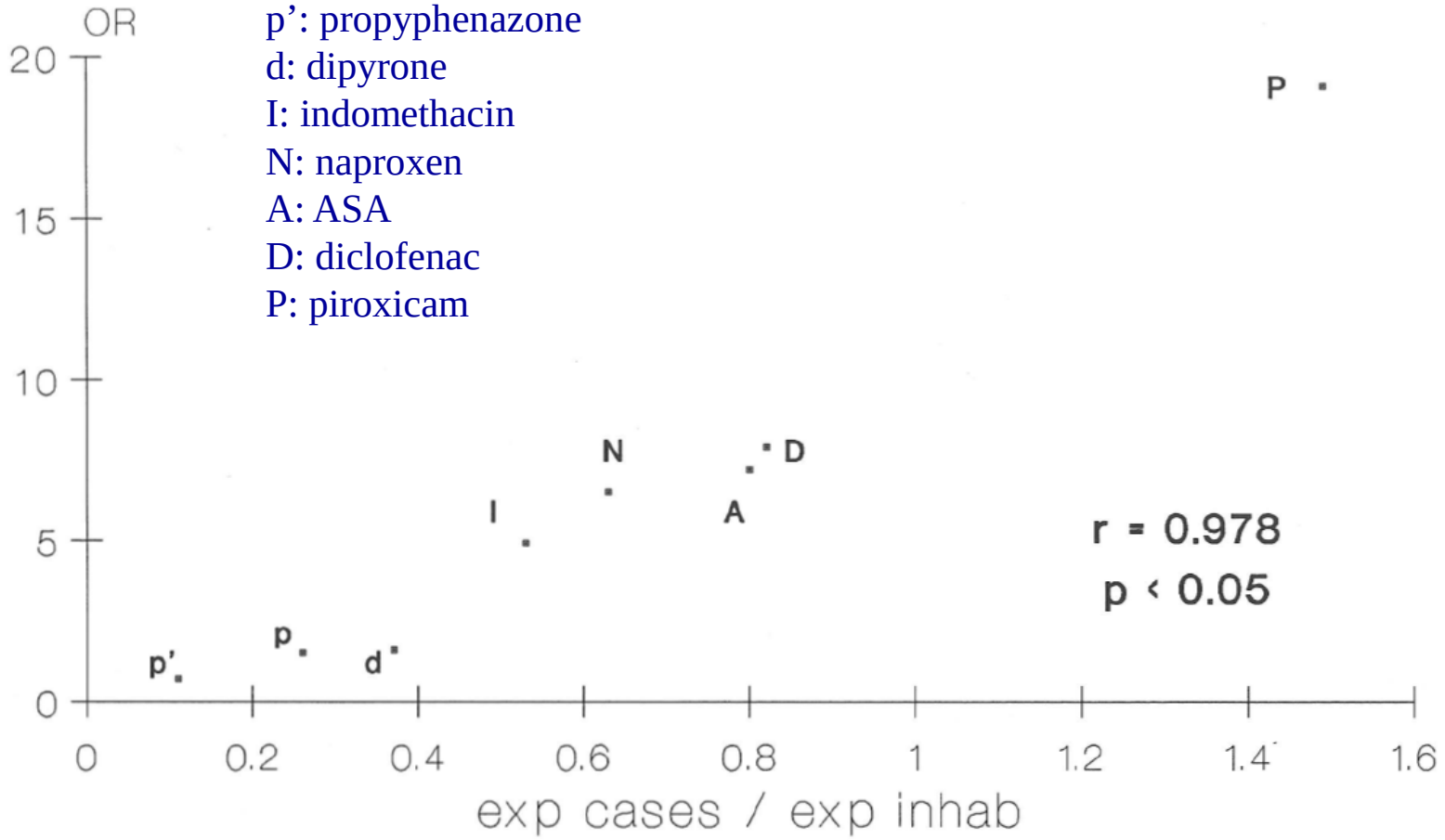
GI bleeding – Case-control *vs* case-population

p: paracetamol
p': propyphenazone
d: dipyrone
I: indomethacin
N: naproxen
A: ASA
D: diclofenac
P: piroxicam



LEADING ARTICLE

Drug Safety 2002; 25 (1): 7-19
0114-5916/02/0001-0007/$25.00/0

Case-Population Studies in Pharmacoepidemiology

Dolors Capellà, Consuelo Pedrós, Xavier Vidal and *Joan-Ramon Laporte*

Fundació Institut Català de Farmacologia, Universitat Autònoma de Barcelona, CSU Vall d'Hebron, Barcelona, Spain

Fundació Institut Català de Farmacologia

Table II. Main characteristics of the 33 studies reviewed

Drug(s) of interest	Disease of interest	Source of patient identification	Information on risk factors and confounding	Source of drug consumption data	Reference
Metoclopramide	Extrapyramidal reactions	SR	SR	IMS	17
Metoclopramide, prochlorperazine	Extrapyramidal reactions	General practitioner[a]	General practitioner[a]	Community pharmacists	18
Phenformin, metformin	All ADRs, with special reference to lactic acidosis	SR	SR + medical records for severe cases	National sales figures + routine nationwide prescription survey	19
Fluoxetine, paroxetine, sertraline	Withdrawal reactions	SR	SR	IMS	20
Zimeldine	Guillain-Barré syndrome certain or highly probable	SR	SR + medical records	National sales figures + routine nationwide prescription survey	21
Piroxicam and 7 other NSAIDs[b]	Upper gastrointestinal bleeding, perforation and ulcer	SR	SR	IMS	22
Acetazolamide	Aplastic anaemia (IAAAS inclusion criteria)	SR	SR + medical records + autopsy data	National sales figures + routine nationwide prescription survey	23
Cotrimoxazole (trimethoprim-sulfamethoxazole)	Leucopenia, agranulocytosis, thrombocytopenia, nonhaemolytic anaemia, combinations, (bicytopenia, tricytopenia) with predefined criteria	SR	SR	National sales figures + routine nationwide prescription survey	24
Sulfasalazine	Agranulocytosis (IAAAS inclusion criteria)	SR	SR	National sales figures + routine nationwide prescription survey	25
Sulphonamide, cotrimoxazole	Agranulocytosis (IAAAS inclusion criteria)	SR + case-control study	SR + medical records + structured questionnaire	National sales figures + routine nationwide prescription survey	26
Dapsone	Agranulocytosis (IAAAS inclusion criteria)	SR	SR	National sales figures + routine nationwide prescription survey	27
Omeprazole, cimetidine, ranitidine	Visual disorders	SR	SR	IMS	28
Erythromycin salts	Hepatotoxicity	SR	SR	National health service prescription data	29
Brodimoprim *vs* amoxicillin, azithromycin, cotrimoxazole, rufloxacin	All ADRs	SR	SR	?	30
Metformin	Lactic acidosis	SR	SR + medical records	National sales figures + routine nationwide prescription survey	31
All drugs	Agranulocytosis, thrombocytopenia, pancytopenia, aplastic anaemia (predefined criteria)	SR	SR	National sales figures + routine nationwide prescription survey	32
All drugs	Aplastic anaemia, agranulocytosis, haemolytic anaemia, thrombocytopenia (predefined criteria)	SR + hospital discharge diagnoses	Medical records	National sales figures + local sample of prescriptions dispensed	33
Chloramphenicol	Fatal aplastic anaemia	Mortality register	Medical records	Registration	
Chloramphenicol	Fatal aplastic anaemia	Mortality register	Medical records	Registration	

Table II. Contd

Drug(s) of interest	Disease of interest	Source of patient identification	Information on risk factors and confounding	Source of drug consumption data	Reference
Phenylbutazone, oxyphenbutazone	Fatal aplastic anaemia	Mortality register + SR	Medical records	National health service prescription data	36
Glafenine*vs* indomethacin, nitrofurantoin, oral penicillins	Anaphylactic reactions (predefined criteria)	Hospital discharge diagnoses	Inquiry to physicians + hospital discharge summaries	Reimbursement figures	37
Glafenine, paracetamol (acetaminophen), amoxicillin, diclofenac, other NSAIDs, penicillins	Anaphylactic reactions (predefined criteria)	Hospital discharge diagnoses	Inquiry to physicians + hospital discharge summaries	Representative sample of pharmacies	38
All drugs	Agranulocytosis (predefined criteria)	Hospital discharge diagnoses	Medical records + inquiry to responsible physicians and pharmacists	Representative sample of pharmacies	39
Dipyrone (metamizole)	Agranulocytosis	Hospital discharge diagnoses	Medical records	IMS	40
Chloramphenicol	Aplastic anaemia	Tertiary referral centre for haematology	Medical records	Registration holders	41
Antiepileptic drugs	Stevens-Johnson syndrome and toxic epidermal necrolysis	Registry	Medical records	?	42
Cinepazide	Agranulocytosis (IAAAS inclusion criteria)	SR + case-control study	SR + structured questionnaire + medical records	National health service prescription data	43
Analgesics and NSAIDs	Upper gastrointestinal haemorrhage	Case-control study	Structured questionnaire + medical records	National health service prescription data + IMS	44
Aprindine	Agranulocytosis (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data	45
Ocular chloramphenicol	Aplastic anaemia (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	Registration holder	46
Nifedipine	Fatal aplastic anaemia (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data	47
Pyrithyldione	Agranulocytosis (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data + IMS	48
Calcium dobesilate	Agranulocytosis (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescriptio	49

Case-population in pharmacovigilance

Rationale

Examples

→ Conclusions

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The case-population strategy

Consists in comparing past exposure to a given risk factor in subjects presenting a given disease or symptom (cases) with the exposure to this factor in the whole cohort or the source population of cases

The case-population strategy

- Need for drug utilization data, which are rarely available
  - IMS
  - National health systems statistics
    - Varying accessibility
    - Rarely offer data on aggregated number of users

http://www.imi-protect.eu/frameworkRep.shtml

PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PROJECT
About PROTECT
Objectives
Governance structure
Partners
Work programme

News

Results

General Presentations

eRoom - partners only

Links
General Links
Collaborations
Training Opportunities
Pregnancy Study
Adverse Drug Reactions Database NEW
Drug Consumption Databases in Europe NEW

FRAMEWORK FOR PHARMACOEPIDEMIOLOGY STUDIES

REPORTS AND DATABASES

Drug Consumption Database

Introduction

Links:

>> Executive Summary

>> **Inventory on Drug Utilisation - MASTER DOCUMENT (version October 2012)**

>> **Inventory on Drug Utilisation - COUNTRIES SUMMARY (version December 2012)**

Back to Results

Characteristics of nationwide administrative databases

Countries	BELGIUM	BULGARIA	CZECH REPUBLIC	DENMARK	FINLAND		FRANCE		GERMANY	HUNGARY
Database name	anet	Not	Not	Register of	Prescription ister base	Drug sales register	ERASME database	ANSM database	WIdO database	Not provided
Data provider	National for Heal Disability (INAMI)		Control		cial rance tution	Finnish Medicines Agency	National Insurance Fund-CNAMTS	The French National Agency for Medicines and Health Products Safety (ANSM)	The Research Institute of the General Medical Insurance Plans (AOK)	Directorate General of National Institute of Pharmacy
Website	www.inami.fgov.be	www.bda.bg	www	aegemid eidstyrelsen.dk	www.kela.fi	www.fimea.fi	www.ameli.fr	www.ansm.sante.fr	http://www.wido.de/	www.ogyi.hu
Accessibility	Application http://www. fgov.be tis ar equest/ind ex.ht	tion ines Control Department maria.popov bda.bg	Application Press and Information Department infs@sukl.cz	Free online www.medstat.dk Further data upon request	Application to KELA research department tutkimus@kela.fi	Application communications@fimea.fi	Application http://www.ameli.fr/l-assurance-maladie/contacts.php	Application communication@ameli.fr	Applicationvalentina.coca@wido.bv.aok.de helmut.schroeder@wido.bv.aok.de	Application ogyi@ogyi.hu
Data source	Re	Sales	Sales (pe 201			rsed	Sales	Reimbursed	Sales	
Healthcare setting	Outpatient		Outpatient	patient	Outpatient	Out/Inpatient	Outpatient	Out/Inpatient	Outpatient	Out/Inpatient
Population coverage	99%	0%		100%		100				
ATC/DDD[a]	Yes	Yes			Yes		Yes	Yes	Yes	Yes
OTC[b]	No	Yes	Yes			s	No	Yes	No	No
Data by age/gender	Yes	No	Yes (since 2011)			No			N	
Record linkage	Yes (within INAMI)	No	No	Yes		No	MTS)		N	

National Health Insurers (6)
National Medicines Agencies (9)
Ministries of Health (3)
Others (4)

ERASME (FR) and WIdO (DE) 85%
Rest of databases 100%

14 databases collect age and gender.
No other clinical information

5 at national level, 1 regional and 2 within health insurer

Database name
Data provider
Website
Accessibility: contact email
Data source
Healthcare setting
Population coverage
ATC/DDD
Data by age and gender
Record linkage

Number of visits to www.imi-protect.eu
(from 1 Jan 2013 until 18 April 2013)

DOCUMENT	VISITS (COMPLETE DOWNLOADS)	VISITS (PARTIAL DOWNLOADS)
DU inventory 2012 COUNTRIES	977	7,954
DU inventory October 2012 MASTER	939	16,043
DU inventory introduction	423	23
DU inventory executive summary	410	50

The case-population strategy

- Need for drug utilization data, which are rarely available
  - IMS
  - National health systems statistics
    - Varying accessibility
    - Rarely offer data on aggregated number of users
- Need for complete ascertainment of cases
  - Setting up collaborating networks in defined areas or using electronic registers of the diagnoses of interest

Methods in pharmacovigilance

- Spontaneous reporting

Anecdotal

Magnitude of association?

No risk estimation

Clinical perspective

- Case-population

Control group

Magnitude of association

Risk estimation

Incidence

Number of cases, population impact

- Case-control studies
- Cohort studies
- (Meta-analysis of) RCTs

Risk estimation

Epidemiological perspective

Incidence

Public health perspective

Strengths	Limitations
• Early signal generation • Incidence • Population impact	• Case ascertainment • Adjusting population denominators • Adjusting exposure denominators • Confounding

Conclusions

- Method for early signal generation
- In certain circumstances, hypothesis generating
- In certain circumstances, early risk estimation and initial estimate of public health impact
- Seems appropriate for type A and type B ADRs
- Need for methodological refinement in relation to:
  - Type A *vs* type B adverse reactions
  - Latency time between exposure and adverse event
  - Etiological fraction of medicines in the condition of interest

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