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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Measuring public health impact of adverse drug reactions

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Outline

Background and Objectives

Methods: Calculation of **Population Attributable Fraction**.

Prevalence of drug exposure
Measures of effect

Results: benzodiazepines-hip fracture
macrolides-induced liver injury

Conclusions
Considerations and final points

Background

- Adverse drug reactions (ADR):
  - morbidity and mortality
- Prevention ADR:
  - effective intervention strategies
- Drug utilisation studies:
  - long-term benefit/risk
  - prevalence of drug use
- Population attributable fraction (PAF)
  - Planning public health interventions

Population attributable fraction

- Proportional reduction in average disease risk

Ø over a specified time interval

Ø that would be achieved by eliminating the exposure of interest

Ø while distributions of other risk factors remain unchanged

Objectives

To assess the public health impact of PROTECT drug-adverse event pairs

Prevalence of drug exposure:

users/10,000-year

Defined Daily Doses/1,000 inh/day (DIDs)

Medical Records (EMR) databases

Healthcare Utilization (HCU) Databases

IMS Health MIDAS database

Effect measures

Systematic Reviews association drug - adverse event pair

POPULATION ATTRIBUTABLE FRACTION

Methods: databases

Databses	HCU	MRs	MIDAS
Description	Drug exposure as part of filling claims for payment. Wholesalers' sales.	Drug exposure as routine collection of clinical data.	Surveys. Commercial data provider: IMS Health.
Drug converge	Prescribed. Reimbursed. Dispensed.	Prescribed by healthcare professional. Prescribed and dispensed.	Sales of medicines from wholesalers and manufacturers.
Type data	Individual-level patient Aggregated data	Individual-level patient.	Aggregated data.
Population coverage	Usually 100%	<10%, representative of the country.	Sample projected at a country level.
PROTECT	ePACT (UK) GIPdatabank (NL) Spanish MoH database (ES)	CPRD, THIN (UK). Mondriaan-NPCRD/AHC (NL). BIFAP (ES).	10 European countries and USA.

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WP2 Framework for pharmacoepidemiological studies
WG3 Drug utilisation data

DRUG CONSUMPTION DATABASES IN EUROPE
Countries summary

First version August 2011
Updated version February 2015

Master document
First version August 2011
Updated version February 2015

SPAIN

Population	46,464,053 inhabitants (1/7/2014). http://www.ine.es/welcoing.htm
Health care provider	Public health sector. Decentralized system with devolved powers to the 17 regions across Spain. Universal access to health services.
Population coverage	99.5%. It includes low-income inhabitants. Civil servants can opt out of the public financed system. 88% of this population and their beneficiaries are covered for-non-for-profit private sector. 13% of the Spanish population are covered by private-for-profit voluntary health insurance, with an important regional variation. Since April 2012, the coverage has been limited requiring residents who earn >100,000 €/year and do not make Social Security contributions to pay for treatment. Undocumented migrants have also been excluded.
Model of health care financing	Highly decentralised model with the allocation of block grants –obtained through taxation-, from the central government to the autonomous communities, except for Navarre and the Basque Country with high autonomy taxation. Taxation represents 94.1% of the funding of the social security system. Out-of-pocket payments.

Reimbursement characteristics

Method of payment	The National Health System (SNS) partially pays reimbursed medicines. Patients pay the rest.
The beneficiaries	All Spanish residents.
Categories of reimbursable drugs	Based on negative lists that exclude pharmaceuticals with low treatment value or not proved to have adequate increased cost-effectiveness. Reimbursement of medicines depends upon the age and income of the patient. Special reimbursement category for people with specific treatments.
Structure of reimbursement to the patient (patient copayment)	*Retired people* pay 10% of the medicines price with a monthly maximum depending on annual income :> €100,000, copayment is 60%; < €18,000 (max per month €8), between ≥€18,000-<€100,000 (max per month €18), ≥€100,000 (max per month €60). *Employees and beneficiaries* copayment rate based on their annual income: < €18,000 40% of the medicines price; >€18,000-<€100,000 50%; >€100,000 (60%). Exemptions for people with toxic syndrome and other disabilities, on social cash aid, retired with non-contributory pensions, unemployed not receiving any social aid, work derived diseases or injuries. For specific treatments copayment is 10% up to a maximum of €4.13/package dispensed. Some food products no copayment after a medical application and approval. There are regional variations.
Reimbursement level for drugs	4 main levels: For employed and their beneficiaries reimbursement rate is between 40 to 60%. For pensioners between a 40-90% is reimbursed. The reimbursement rates depend on annual income. For specific treatments, reimbursement is 90%.

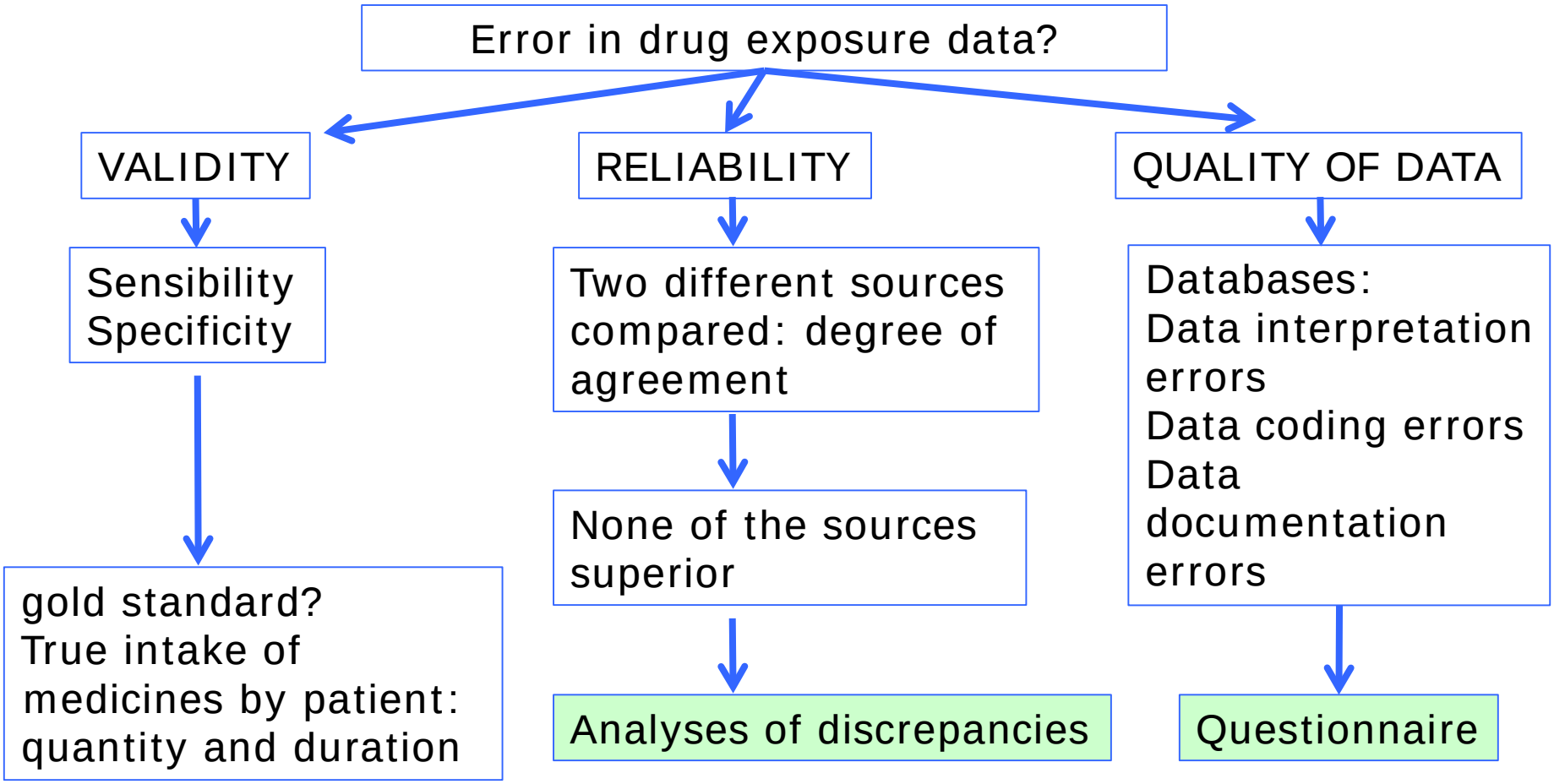
National drug consumption database: DGFPS database

Organisation	Ministry of Health, Social Policy, and Equity. DGFPS: Dirección General de Farmacia y Productos Sanitarios (General Directorate of Pharmacy and Health Products).
Web	www.msc.es/profesionales/farmacia/organizacion.htm
Source	Drugs dispensed by community pharmacies reimbursed by the National Health System. Data is collected at regional level and centralised in the Ministry of Health. Not included are medicines consumption reimbursed by other health insurances that specifically cover civil servants or military personnel.
Setting	Outpatient.
Population coverage	95%.
Accessibility	Application to data provider sede@msssi.es (If of interest, data may be applied for at regional level with a list of the regional health authorities available on the website).
Drug codification	ATC code.
Data	Region, DDD, turnover, prescriber's code, national pharmaceutical code, pharmacist's code, strength, dosage form. Some regions collect data on age and gender.
Record period	Since 1985 (computerised data).
Language	Spanish.
Record linkage	No.

List of national websites of interest

National Medicine Agency	Agencia Española de Medicamentos y Productos Sanitarios-AEMPS. Spanish Agency for Medicines and Medical Devices.	www.aemps.gob.es
Pricing Agency	Ministerio de Sanidad , Política Social e Igualdad. Dirección General de Farmacia y Productos Sanitarios. Ministry of Health and Social Policy. Directorate of Pharmacy and Health Products.	www.msc.es/profesionales/farmacia/organizacion.htm
Reimbursement Agency	Ministerio de Sanidad, Política Social e Igualdad. Dirección General de Farmacia y Productos Sanitarios. Ministry of Health and Social Policy. Directorate of Pharmacy and Health Products.	www.msc.es/profesionales/farmacia/organizacion.htm
Pharmaceutical data source	Consejo General de Colegios Oficiales de Farmacéuticos. General Council of the Official Pharmaceutical Professional Association. Database with information about drugs by region.	https://botplusweb.portalfarma.com/ (No free access).
	Agencia Española de medicamentos y productos sanitarios (AEMPS). CIMA database.	http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm

Methods: validity drug consumption data



Methods: Discrepancies between HCU and MRs databases

	HCU databases	MRs databases
Databases	ePACT (UK) GIPdatabank (NL) Spanish MoH database (ES)	CPRD, THIN (UK). Mondriaan-NPCRD/AHC (NL). BIFAP (ES).
Drug coverage	Reimbursed	Prescribed Prescribed and dispensed (Mondriaan NPCRD)
Outcome	DDD/1,000 inhabitants /day à apparent users (AU) AU=DID x 365/d (recommended treatment period)	One-year period prevalence rates (PPRs): users/1,000 people-year
Year of study	2008	2008
Statistical analyses	Percentage differences, correlation coefficient, Bland Altman plots (level of agreement). Stratification: ATC level 3 (Calcium channel blockers, antiepileptic drugs à chronic use). ATC level 4 (Macrolides, benzodiazepines, antidepressants à short/ intermittent use).	

Methods:
Discrepancies between HCU and MR databases

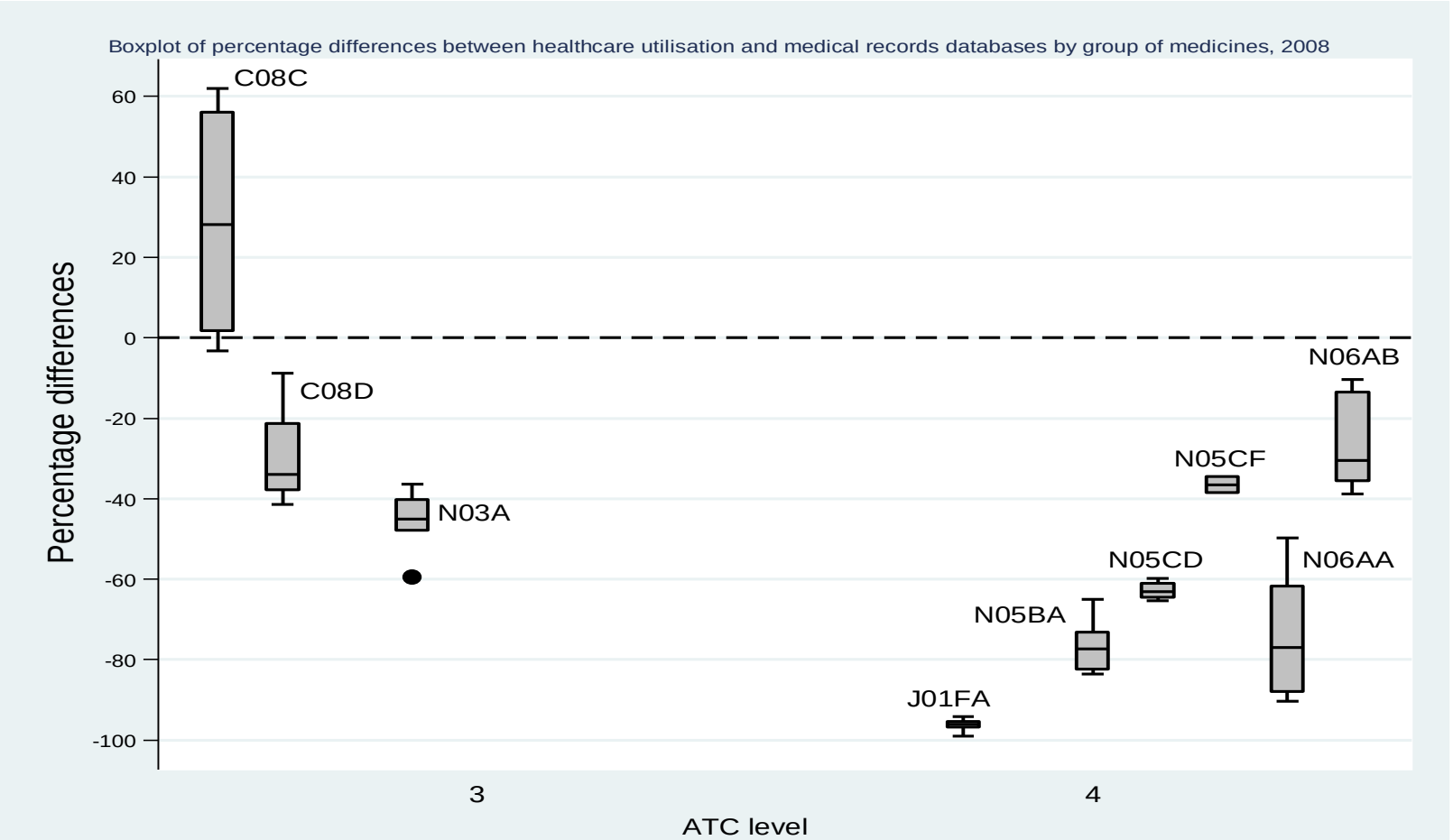
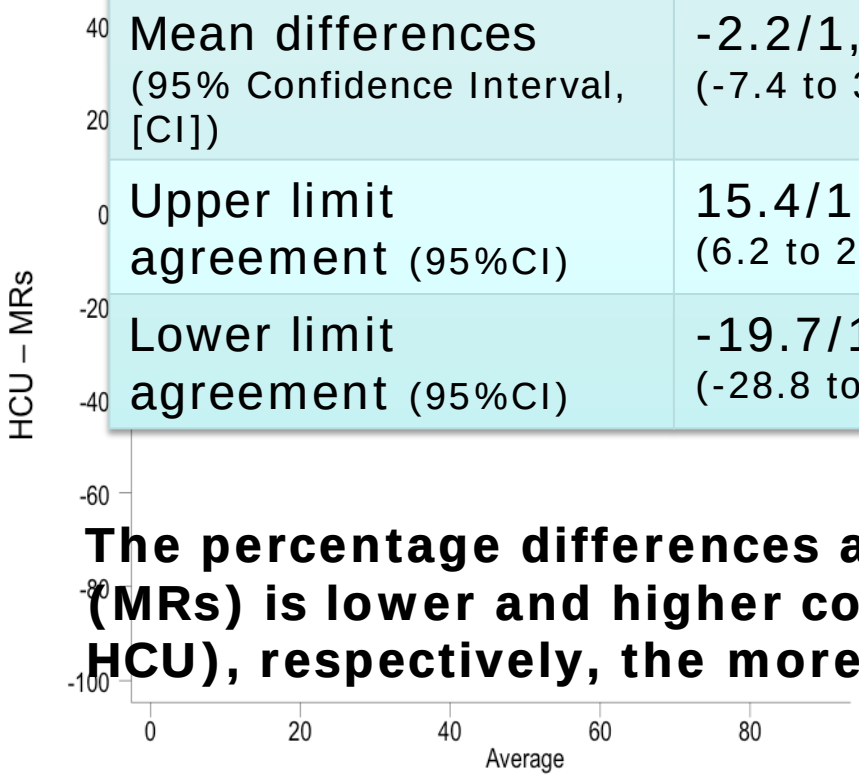


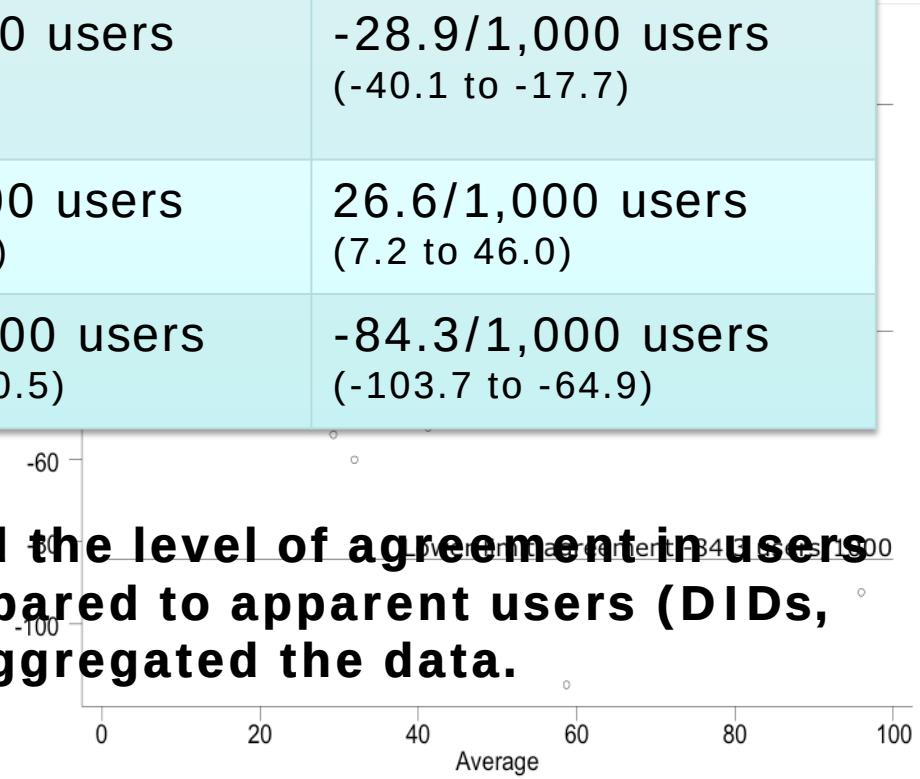
Figure 1. Boxplot of percentage differences between healthcare utilisation and medical records databases by group of medicines, 2008. ATC level 3: calcium channel blockers (C08C, C08D), and antiepileptic drugs (N03A). ATC level 4: macrolides (J01FA), hypnotics and sedatives (N05CD, N05CF), anxyolytics (N05BA), tricyclic antidepressants (N06AA) , and selective serotonin reuptake inhibitors (N06AB).

Methods:
Discrepancies between HCU and MR databases

Correlation coefficient:
ATC level 3: r=0.88, p<0.001 ATC level 4: r=0.51, p=0.008

Bland Altman plot	ATC level 3	ATC level 4
Mean differences (95% Confidence Interval, [CI])	-2.2/1,000 users (-7.4 to 3.1)	-28.9/1,000 users (-40.1 to -17.7)
Upper limit agreement (95%CI)	15.4/1,000 users (6.2 to 24.5)	26.6/1,000 users (7.2 to 46.0)
Lower limit agreement (95%CI)	-19.7/1,000 users (-28.8 to -10.5)	-84.3/1,000 users (-103.7 to -64.9)





The percentage differences and the level of agreement in users (MRs) is lower and higher compared to apparent users (DIDs, HCU), respectively, the more aggregated the data.

Methods: PAF calculation

SOURCES OF PREVALENCE OF DRUG EXPOSURE
Benzodiazepines-hip fracture: • IMS MIDAS database: DIDs converted into users through conversion factor (average users/average sales volume in Denmark, Norway and Netherlands). **Macrolides and induced hepatotoxicity**: • Medical record databases: users/1,000: CPRD and THIN (United Kingdom), Mondriaan databases (Netherlands), BIFAP (Spain), Bavarian Statutory Health Insurance (Germany).

SOURCES OF EFFECT MEASURES
Meta-analysis of results systematic review

Methods: PAF calculation

Benzodiazepines-hip fracture

$PAF = P_e(RR-1)/P_e(RR-1)+1$ ⌘

P_e prevalence of exposure to the drug; RR relative risk

Macrolides-hepatotoxicity

$PAF = P_O\ (RR_a-1)/\{P_O(RR_a-1)+1\} = (RR_a-1)/(RR_a+1/O_O)$ §

O_O, estimated prevalence odds: $P_e/(1-P_e)$ and RR_a, the adjusted relative risk

⌘ Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9:531-41.
§ Greenland S. Interval estimation by simulation as an alternative to and extension of confidence intervals. Int J Epidemiol 2004; 33:1389-94.

Results: benzodiazepines-hip fracture

Any benzodiazepines	Country	DIDs	PAF (95%CI)
RR=1.40 (1.24-1.58) I^2=66% P<0.0001	France	76.0	7.4% (4.5-10)
	Germany	18.0	1.8% (1.1-2.6)
	Italy	52.4	5.2% (3.2-7.3)
	Spain	85.5	8.2% (5.1-12)
	UK	19.3	2.0% (1.2-2.8)
	USA	82.9	8.0% (4.9-11)

Khong TP, de Vries F, Goldenberg JSB, Klungel OH, Robinson NJ, Ibáñez L, et al. Potential impact of benzodiazepine use on the rate of hip fractures in five large European countries and the United States. Calcif Tissue Int [Internet]. 2012;91:24–31.

Results: benzodiazepines-hip fracture

Category	Country	DIDs	PAF (95% CI)
Short-acting BZD	France	64.1	3.7% (1.5-6.1)
RR=1.23 (1.09-1.39) I^2=46% P=0.0006	Germany	14.0	0.8% (0.3-1.4)
	Italy	42.4	2.5% (1.0-4.1)
	Spain	67.9	3.9% (1.6-6.4)
	UK	11.6	0.7% (0.3-1.2)
	USA	75.9	4.3% (1.7-7.1)
Long-acting BZD	France	11.9	1.0% (0.3-1.8)
RR= 1.32 (1.10-1.58) I^2=42% P=0.003	Germany	3.9	0.3% (0.1-0.6)
	Italy	10.0	0.8% (0.3-1.5)
	Spain	17.6	1.5% (0.5-2.6)
	UK	7.6	0.6% (0.2-1.2)
	USA	7.0	0.6% (0.2-1.1)

Khong TP, de Vries F, Goldenberg JSB, Klungel OH, Robinson NJ, Ibáñez L, et al. Potential impact of benzodiazepine use on the rate of hip fractures in five large European countries and the United States. Calcif Tissue Int [Internet]. 2012;91:24–31.

Results: macrolides-hepatotoxicity

Macrolides	Country	Estimated Pe (x1,000)	PAF (95%CI)
RR=3.80 (2.20-6.55) I^2=64% P<0.0001	Germany Bavarian claims database	62.6	18.4%(10.3-25.7)
	Spain BIFAP database	62.1	18.3%(10.2-25.6)
	UK CPRD database	48.2	14.8% (8.1-21.0)
	UK THIN database	56.3	16.8% (9.3-23.7)
	Netherlands NPCRD database	21.7	7.2% (3.7-10.6)
	Netherlands AHC database	116.2	29.5% (18.0-39.4)

Ferrer et al. Macrolides and amoxicillin clavulanate-induced hepatotoxicity. https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMIPROTECT/0_f717c/FerrerP. et al; Macrolides and Amoxicillinclavulanate-induced acute hepatotoxicity;Drug Safety; May2014.docx

Considerations (1)

Scenarios for public health action:

1. Common outcome:

benzodiazepines-hip fracture

Low rate ratio and high prevalence of exposure

A small PAF may mean many cases could potentially be prevented.

2. Rare outcome: ALI

macrolides-induced liver injury

High rate ratio and high prevalence of exposure

A high PAF: a few cases of hepatotoxicity could potentialy be prevented.

Considerations (2)

Causal relationship

Bias in the estimation of PAF:

- Prevalence of drug exposure
- RR calculation
- Formula to calculate PAF and 95%CI

CAUSAL RELATIONSHIP:

1. Proportion of the ADR burden causally explained by the drug:
   No availability of individual-patient level data precluded the consideration of confounders and effect modifiers in PAF calculation.

Considerations (3)

Causal relationship

Bias in the estimation of PAF:

- Prevalence of drug exposure
- RR calculation
- Formula to calculate PAF and 95%CI

CAUSAL RELATIONSHIP:

2. Proportion of the ADR that would be eliminated or reduced from the population if the exposure to the drug was eliminated or reduced.

   Importance of the intervention to eliminate the exposure.

Considerations (4)

Causal relationship

Bias in the estimation of PAF:

Prevalence of drug exposure

RR calculation

Formula to calculate PAF and 95%CI

BIAS IN PREVALENCE OF DRUG EXPOSURE:

DIDs converted into users: calculated with the average users/average sales volume from Denmark, Norway and Netherlands.

MRs databases: representative of the target population.

Broad definition of exposure: ever exposed vs never exposed.

Considerations (5)

Causal relationship

Bias in the estimation of PAF:

prevalence of drug exposure

RR calculation

Formula to calculate PAF and 95%CI

BIAS IN THE RR CALCULATION: HETEROGENEITY META-ANALYSES

Inclusion of observational studies: moderate to considerable heterogeneity (I^2) à limits generasibility of results.

No system for grading of the evidence.

Considerations (6)

Causal relationship

Bias in the estimation of PAF:

prevalence of drug exposure

RR calculation

Formula to calculate PAF and 95%CI

FORMULA TO CALCULATE PAF AND 95%CI

Extensive bibliography on formulas to calculate the PAF and 95%CI.

Two different approaches: Levin's formula and substitution method

Greenland's approach to consider the 2 independent sources of information.

Final points

PAF as a starting discussion point of the public health consequences of intervening to reduce the prevalence of a particular exposure

Thank you

Members of PROTECT WP2

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