PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Lessons learned from PROTECT on common protocols for multi-database studies

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Disclosures

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PROTECT Goal

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

These methods are being tested in real-world situations

Main objectives

- Explain differences in drug-adverse event associations due to choices in methodology and databases
- Replication program of studies
  - Same study EU database
  - Different study database, specifically US data source

Abbing-Karahagopian V, et al. Curr Clin Pharmacol 2014;9:130-8

Drug-AE pairs and designs

Drug-AE pair	Descriptive	Cohort	Nested case control	Case crossover	Self-Controlled case series
AB-ALI	All Databases	CPRD BIFAP	CPRD BIFAP	CPRD	CPRD
AED-Suicidality	All Databases	CPRD DKMA			
AD- Hip	All Databases	THIN Mondriaan BIFAP	THIN Mondriaan BIFAP	THIN Mondriaan	THIN Mondriaan
BZP-Hip	All Databases	CPRD BIFAP Mondriaan	CPRD BIFAP Mondriaan	CPRD BIFAP	CPRD BIFAP
B2A-AMI	All Databases	CPRD Mondriaan			
CCB-Cancer	All Databases	CPRD			

Characteristics of healthcare databases

Database	Country	Cumulative population (2008)	Active population (2008)	Data source	Coding diagnoses	Coding drugs	Recording of drug use
BIFAP	ES	3.2 Mio	1.6 Mio	GP	ICPC	ATC	Prescribing
CPRD	UK	11.0 Mio	3.6 Mio	GP	READ	BNF	Prescribing
THIN	UK	7.8 Mio	3.1 Mio	GP	READ	BNF	Prescribing
Mondriaan	NL						
NPCRD		0.7 Mio	0.34 Mio	GP	ICPC	ATC	Prescribing
AHC		0.26 Mio	0.17 Mio	GP/Pharmacy	ICPC	ATC	Prescribing + dispensing
The Danish national registries	DK	5.2 Mio	5.2 Mio	Hospital/ Pharmacy	ICD-8/10	ATC	Dispensing
PGRx	FR/ UK/ CN	10 k	10 k	GP + Specialist Registries	ICD-9	ATC/ EPH MRA	Prescribing + Patient Interview
Clinformatics	US	47 Mio	15 Mio	Claims health insurance	ICD-9	NDC	Claims

Procedures

- Common protocol for each drug-AE pair
  - Extensive sensitivity analyses on main methodological issues
- Common standards, templates, procedures
  - Detailed data specification including definitions of exposures, outcomes, and confounders for each database.
- Blinding of results of in-parallel and replication analyses
  - Stepwise unblinding after completion of each design
- Registration of protocols at ENCePP to guarantee transparency

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2015)
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ORIGINAL REPORT

Hip/femur fractures associated with the use of benzodiazepines (anxiolytics, hypnotics and related drugs): a methodological approach to assess consistencies acro

Gema Requena[1†], Consuelo Huerta[2*,†]
Victoria Abbing-Karahagopian[3], Monts
Ana Afonso[3], Nada Boudiaf[5], Elisa Ma
Saga Johansson[9], Raymond Schlienger

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2015)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3822

ORIGINAL REPORT

Do case-only designs yield consistent results across design and different databases? A case study of hip fractures and benzodiazepines[†]

Gema Requena[1*,‡], John Logie[2‡], Elisa Martin[3], Nada Boudiaf[2], Rocío González González[3], Consuelo Huerta[3], Arturo Alvarez[3], David Webb[2], Andrew Bate[4], Luis A. García Rodríguez[5], Robert Reynolds[6], Raymond Schlienger[7], Helga Gardarsdottir[8], Mark de Groot[8], Olaf H. Klungel[8], Fancisco de Abajo[1,9] and Ian J. Douglas[10]

Table 1. Baseline demographics and characteristics of patients initiating prescription of anxiolytic or hypnotic medication

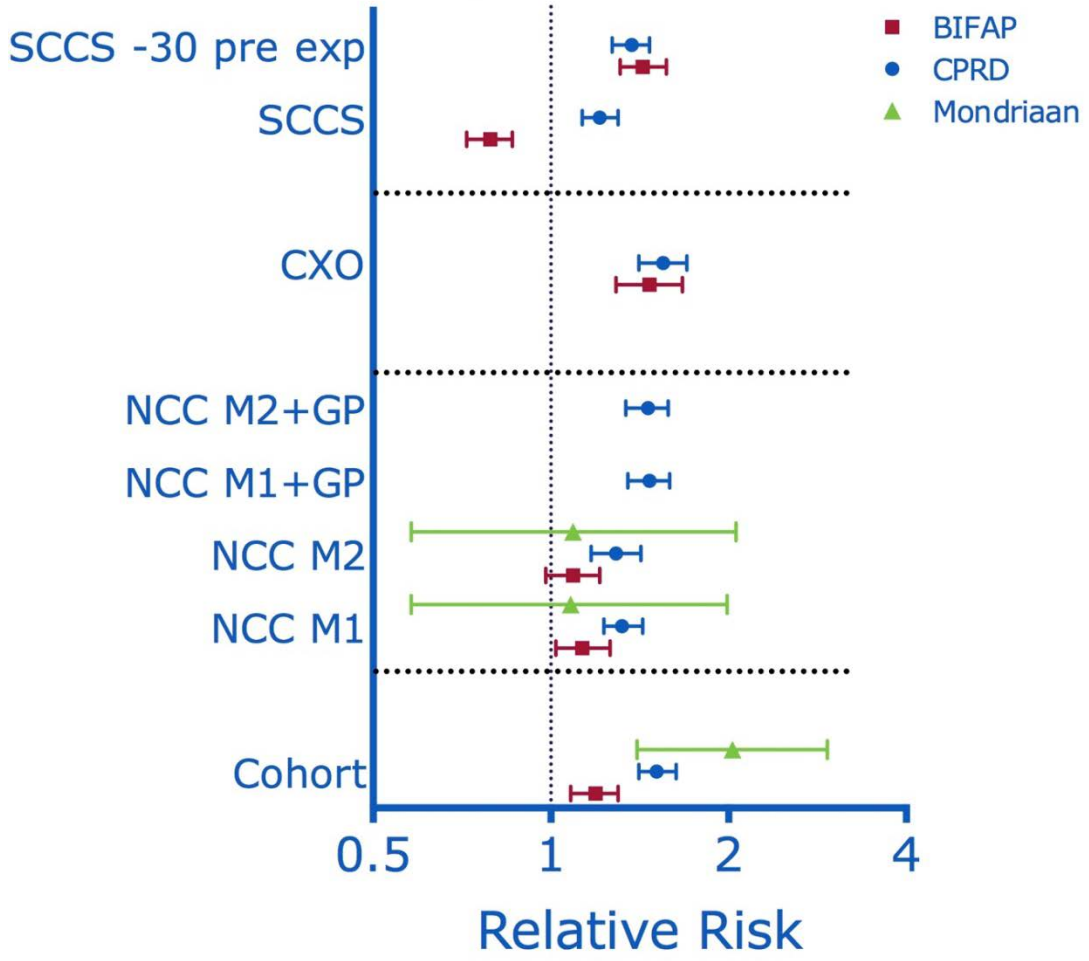
	BIFAP	CPRD	MONDRIAAN
	N = 558 599	*N* = 663 894	*N* = 50 464
Duration of follow-up (after start date) years	1 695 045	2 430 138	146 455
	n (%)		
Age, year Mean (SD)	55.14 (18.7)		
18–29	75 264 (13.5)		
30–39	105 270 (18.8)		
40–49	107 332 (19.2)		
50–59	98 620 (17.7)		
60–69	71 976 (12.9)		
70–79	62 765 (11.2)		
80+	37 372 (6.7)		
Sex			
Male	192 519 (34.5)		
Female	366 080 (65.5)		
Smoking			
Yes	84 224 (15.1)		
No	173 543 (31.1)		
Past	8240 (1.5)		
Unknown	292 592 (52.4)		
Alcohol use			
Yes			
No	133 628 (20.1)	—	

Table 1. (Continued)

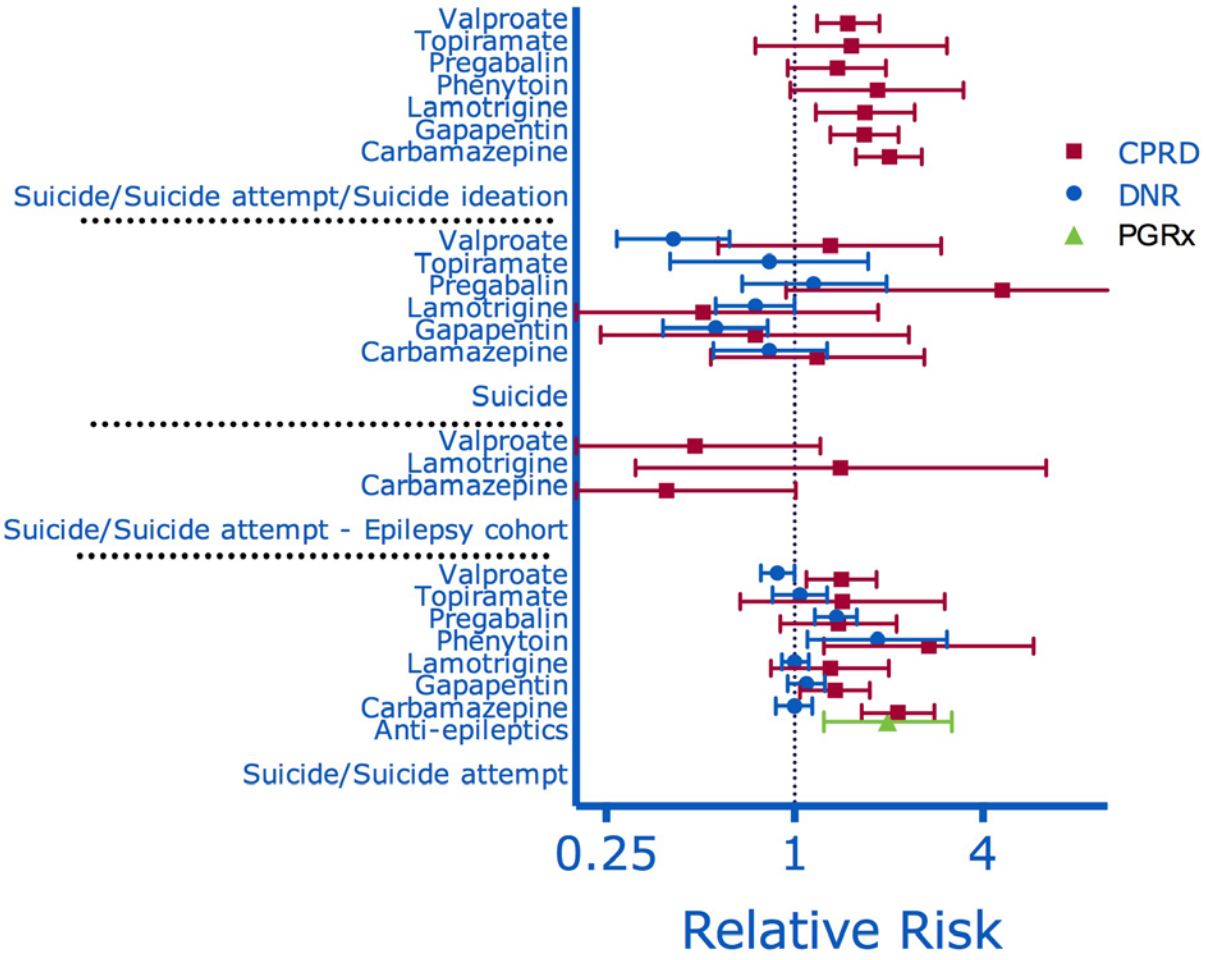
	BIFAP	CPRD	MONDRIAAN
	N = 558 599	*N* = 663 894	*N* = 50 464
Unknown		98 652 (14.9)	—
BMI (kg/m^2)			
<18.5	3838 (0.7)	14 816 (2.2)	—
18.5–24.9	69 796 (12.5)	228 910 (34.5)	—
25–30	92 072 (16.5)	180 089 (27.1)	—
>30	74 693 (13.4)	115 113 (17.3)	—
Unknown	318 200 (57.0)	124 966 (19.8)	—
Co-morbidity			
Previous fractures	24 635 (4.4)	129 519 (19.5)	2212 (4.4)
Rheumatoid arthritis	2886 (0.5)	10 363 (1.6)	0 (0)
Osteoporosis	22 494 (4.0)	16 710 (2.5)	596 (1.2)
Paget's disease	432 (0.1)	690 (0.1)	
Anemia	34 196 (6.1)	48 698 (7.3)	1676 (3.3)
Epilepsies/ seizures	5013 (0.9)	20 553 (3.1)	493 (1.0)

(Continues)

Benzodiazepines and risk of Hip Fracture



Antiepileptics and suicide



Challenges / lessons learned

- **Substantial time** (+/-1 year) reach agreement on common protocol
  - Consensus/buy-in on approach between stakeholders!
- Research question determined **choice of database and design** of data collection
- **Detailed data-specification** documents are needed to harmonize procedures and analyses
- **Frequent communication** between research centres to reduce variation in "interpretation" of protocol
- During programming and analysis phase **further clarification** is required and needs documentation

Methodological determinants of drug-AE associations

- Databases
- Study design
- Outcome definition
- Exposure definition
- Methods to control for confounding

Recommendations

- Develop common protocol with great detail to reduce methodological differences and “interpretation” by researchers
- Solid infrastructure for communication/collaboration
- Conduct analysis in parallel in multiple DBs versus “a priori” pooling of DBs
  - Cherish heterogeneity and explore its sources

Recommendations

- To test robustness of findings conduct multiple sensitivity analyses:
  - Multiple designs (e.g. Cohort/case-control vs case-only)
  - Exposure (e.g. Individual AEDs), outcome (e.g SUI), confounding adjustment
- Replication needed if parallel analysis consistent?

What's next ?

- Network for observational safety and effectiveness studies
  - Common protocol in multiple databases may increase confidence in investigations
  - Testing of existing network
    - New safety signals
    - Platform for methods development and testing
  - Further development of network infrastructure
    - Library of codes/programs
    - Governance of network
    - Structure for collaboration/communication
    - **Collaboration with other networks**

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