



# Farmakoepidemiologi: metoder og mål

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# Hvad er farmakoepidemiologi

Epidemiologi:

"An empirical science dedicated to the study of occurrence and determinants of disease in populations" Rothman

Farmakoepidemiologi:

"The study of the use of and the effects of drugs in large numbers of people" Strom

El. klinisk farmakologiske problemer, belyst ved epidemiologiske metoder. Oftest observationelle undersøgelser



# Hvorfor farmakoepidemiologi?

- Enhver skadelig lægemiddelvirkning kan forveksles med spontant opstået sygdom
- Før markedsføring har lægemidler været anvendt på 3000-5000 patienter
- Ethiske problemer i at studere skadevirkninger ved kliniske forsøg
- 1-3% af alle lægemidler trækkes tilbage på grund af skadevirkninger som ikke var kendt på markedsføringstidpunktet
- Heller ikke alle gavnlige virkninger er kendt ved markedsføring
- En del lægemidler anklages uberettiget for at have skadevirkninger
- Lægemidler bruges ikke af de personer og på den måde, som det var tiltænkt.



# Overset problem: SSRI og maveblødning

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## Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study

Francisco José de Abajo, Luis Alberto García Rodríguez, Dolores Montero

### *Editorial*

by Li Wan Po

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Centro Español de Investigación

de Abajo et al. BMJ 1999.

### Abstract

**Objective** To examine the association between selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding.

**Design** Population based case-control study.

**Setting** General practices included in the UK general practice research database.

**Subjects** 1651 incident cases of upper gastrointestinal bleeding and 248 cases of ulcer perforation among patients aged 40 to 79 years between April 1993 and September 1997, and 10 000 controls matched for age, sex, and year that the case was identified.

**Interventions** Review of computer profiles for all potential cases, and an internal validation study to confirm the accuracy of the diagnosis on the basis of the computerised information.

**Main outcome measures** Current use of selective serotonin reuptake inhibitors or other antidepressants

### Introduction

In the past few years several case reports have shown an association between selective serotonin reuptake inhibitors such as fluoxetine and bleeding disorders.<sup>1-7</sup> Most of the patients had mild bleeding disorders, for example, ecchymoses, purpura, epistaxis, or prolonged bleeding time but several had more serious conditions such as gastrointestinal haemorrhage, genitourinary bleeding, and intracranial haemorrhage.<sup>5-6</sup>

The release of serotonin from platelets has an important role in regulating the haemostatic response to vascular injury.<sup>8,9</sup> Serotonin is not synthesised in platelets but is taken up from the circulation by serotonin transporters on the platelets, which are similar to those in the human brain.<sup>10</sup> At therapeutic doses fluoxetine and other selective serotonin reuptake inhibitors have consistently been shown to block this reuptake of serotonin by platelets leading to a



# Falsk problem: Sildenafil (Viagra™) og hjertetilfælde

RESEARCH LETTERS

## Research letters

### Acute myocardial infarction associated with sildenafil

*J Feenstra, R J H M van Drie-Pierik, C F Laclé, B H Ch Stricker*

Sildenafil has been registered in the USA for the treatment of erectile dysfunction; and on Sept 15 was approved by the European Medicines Evaluation Agency. Sildenafil acts by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP) by cGMP-specific phosphodiesterase 5.<sup>1</sup> Increased concentration of cGMP in the smooth-muscle cells of the corpora cavernosa leads to smooth-muscle relaxation and vasodilatation which is essential for normal erection. Adverse effects of sildenafil include headache, flushing, dyspepsia, nasal congestion, and visual disturbances.<sup>2</sup> We report a patient who developed an acute myocardial infarction after taking one tablet of sildenafil.

A 65-year-old man was admitted to hospital at 0000 h complaining of 1 h of acute severe left-sided chest pain, nausea, and vomiting which started approximately 30 min after he took one tablet of sildenafil 50 mg and before any attempt at sexual intercourse. He had never used sildenafil before. Sildenafil had been prescribed by a doctor in the USA and obtained from a pharmacy after a medical check-up at which his physical examination and blood pressure were normal, but no electrocardiogram was recorded. His history revealed no diabetes mellitus, hypertension, pre-existing cardiovascular disease, or previous episodes of chest pain. His height was 1.7 m and weight 81 kg (body-mass index: 28). He had never smoked tobacco and took

present. At 7 and 2 min before the electrocardiogram, he was given glyceryl trinitrate 0.4 mg sublingually with some relief of his chest pain. Acute anterior myocardial infarction was diagnosed, and he was given 500 mg acetylsalicylic acid, 5000 IU followed by 25 000 IU/24 h of intravenous heparin, 0.1 mg of intravenous fentanyl, and an intravenous bolus of 15 mg recombinant tissue plasminogen activator, followed by 0.75 mg/kg per 30 min and subsequently 0.5 mg/kg per 60 min to a total of 100 mg. Within 24 h, CK reached a maximum concentration of 5222 U/L, and LDH and ALT increased to 2078 U/L and 75 U/L. His serum total cholesterol was 4.3 mmol/L (normal <5.2 mmol/L) with a slightly low HDL-cholesterol of 0.8 mmol/L (normal >0.9 mmol/L). Serum LDL-cholesterol and serum triglycerides were 3.2 mmol/L (normal <3.4 mmol/L) and 0.79 mmol/L (normal <1.8 mmol/L). Echocardiography, 5 days after admission, showed an apical aneurysm and a left-ventricular ejection fraction of 40%. He recovered without complications.

The close temporal relation between ingesting sildenafil and onset of severe chest pain due to acute myocardial infarction in a patient without a history of previous chest pain or risk factors for cardiovascular disease such as diabetes mellitus, hypertension, smoking, or hypercholesterolaemia, suggests that sildenafil was causally related to the acute myocardial infarction. Since the chest



# Overset (?) problem: Vioxx™ og hjertetilfælde, kumuleret meta-analyse

Peter Jûni et al.  
Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004

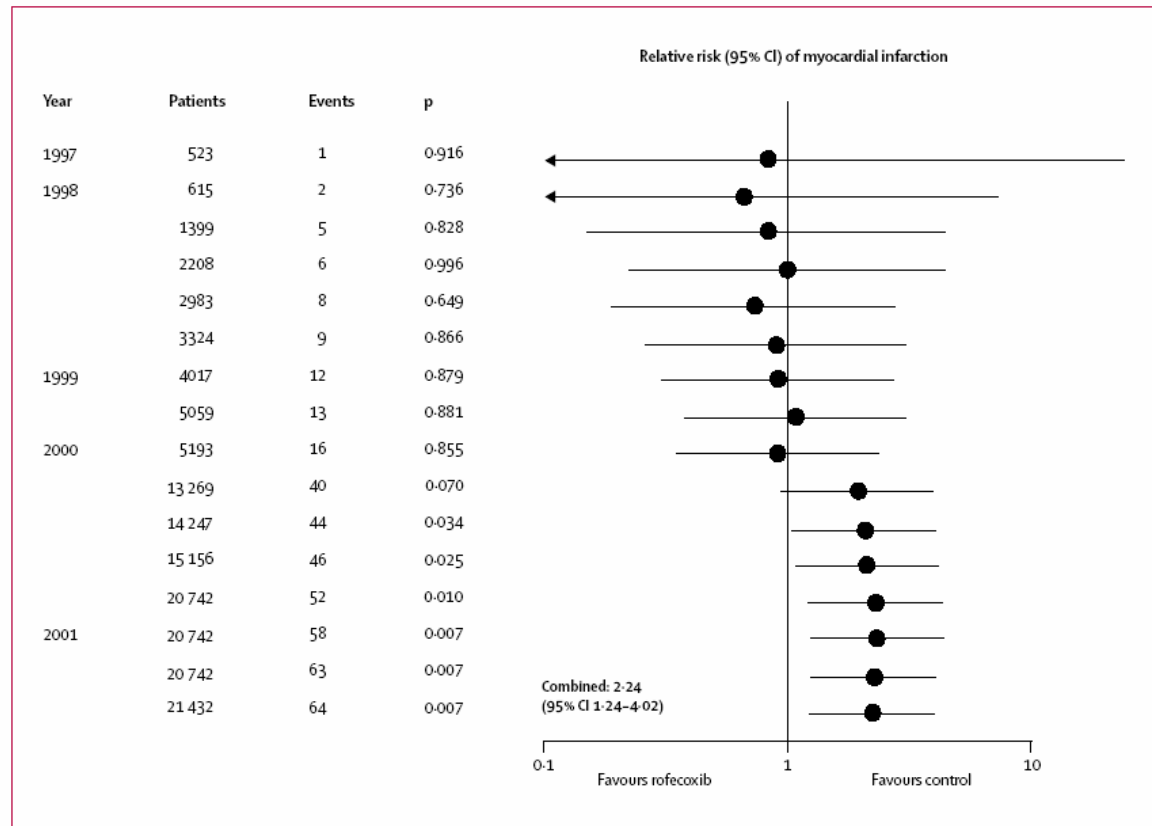
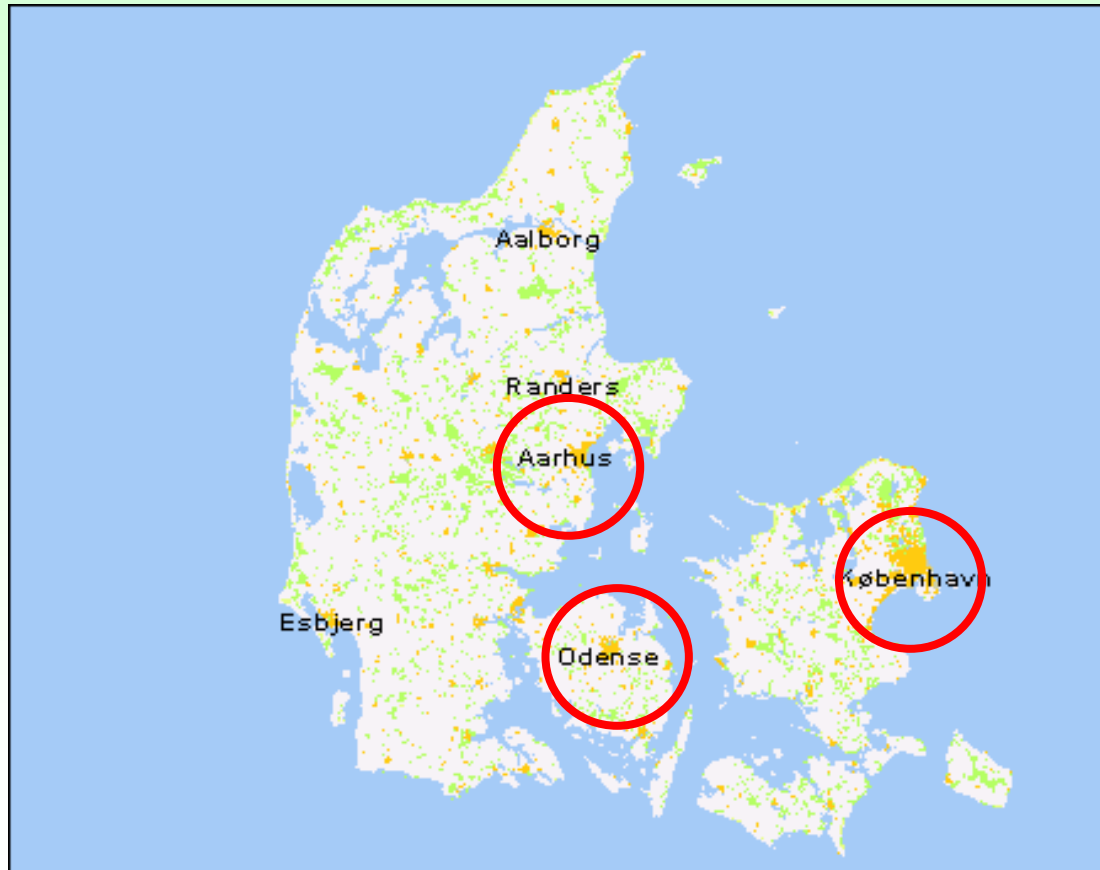


Figure 3: Cumulative meta-analysis of randomised trials comparing rofecoxib with control  
See figure 2 for sequence of trials.



# Farmakoepidemiologiske miljøer i Danmark





# Farmakoepidemiologiske miljøer i Danmark

Miljø	Region	Studiebase	Siden	Fokus
Odense	Fyns amt Vestsj. amt	0,8 mio	1990	Klinisk Farmaologi
Århus	Nord- Jylland Viborg Århus	1,4 mio	1989	Klinisk Epidemiology
Lægemiddel- styrelsen	Danmark	5,4 mio	1994	Administrativ/ Regulatorisk / Forskning



# OPED, status

>40 mio personidentificerbare receptregistreringer

Status som offentligt forskningsregister med SDU, Odense Universitet som registeransvarlig

Vedligeholdes af Center for Klinisk Farmakologi Odense, SDU

Data kan udleveres til andre forskere efter godkendelse fra Datatilsynet



# Prescription Database of Northern Jutland (PDNJ)

Dækker

- Nordjyllands Amt
- Århus Amt
- Viborg Amt

Dækker samme variable som OPED

Mulighed for kobling til diagnoseregistre og andre registre

Status som privat forskningsregister under Århus Universitet, Afd.  
For klinisk Epidemiologi



# Lægemedelstyrelsens receptregister

- Lovfæstet i 1993
- Virksomt fra 1994
- Dækker alle 288 danske apoteksudsalg og alle sygehusapoteker, i alt 5,2 millioner personer
- Individbaseret, ved brug af irreversibel, entydige kryptering af CPR-numrene.
- Dækker både tilskudsberettigede og ikke-tilskudsberettigede lægemidler
- Oprettet til administrative formål, ikke forskning
- Leverer detaljeret individbaseret lægemiddelstatistik



# Lægemedelstyrelsens statistik

## Statistik grupperet efter lægemiddelstof, 2000-2004

Sektor

Primær sundhedssektor

Søg på handelsnavn

ATC-gruppe

C10AA03 : Pravastatin

Søg på indholdsstof

Region

Fyns Amt

Aldersgruppe

40-44

Køn

Mænd

Oplysning

Antal personer i behandling

Ny søgning

Excel version

Print

Antal personer i behandling, Mænd, 40-44 år, Fyns Amt, Primær s

ATC gruppe	Lægemedelgruppe / indholdsstof	2000	2001	2002	2003	2004
		Antal personer i behandling				
C10AA03	Pravastatin	26	28	33	38	28



## Lægemiddelstyrelsens register i Danmarks Statistik

- Rummer hele Lægemiddelstyrelsens receptregister siden 1995
- Rummer hele LPR
- Linkage mulig via krypteret CPR-nummer
- Adgang til data via sikker kobling
- Individbaserede oplysninger udleveres ikke
- Færdige analyser sendes pr. e-mail til forskeren
- Forskerserviceenhed
- Kontakt: [www.dst.dk/forskning](http://www.dst.dk/forskning)



*Epilepsia*, 45(11):1330–1337, 2004  
Blackwell Publishing, Inc.  
© 2004 International League Against Epilepsy

## Clinical Research

# Fracture Risk Associated with Use of Antiepileptic Drugs

Peter Vestergaard, Lars Rejnmark, and Leif Mosekilde

*Department of Endocrinology and Metabolism, Aarhus University Hospital, Aarhus Sygehus, Aarhus, Denmark*

**Summary:** *Purpose:* To assess fracture risk associated with different antiepileptic drugs (AEDs). An increased fracture risk has been reported in patients with epilepsy. Classical AEDs have been associated with decreased bone mineral density. The effects of newer AEDs are unknown.

*Methods:* We undertook a population-based pharmacoepidemiologic case-control study with any fracture as outcome and use of AEDs as exposure variables (124,655 fracture cases and 373,962 controls).

*Results:* All AEDs were associated with an increased fracture risk in an unadjusted analysis. After adjustment for prior fracture, use (ever) of corticosteroids, comorbidity, social variables, and diagnosis of epilepsy, carbamazepine [CBZ; odds ratio (OR), 1.18; 95% confidence interval (CI), 1.10–1.26], [and oxcarbazepine (OXC; 1.14, 1.03–1.26)], clonazepam (CZP; 1.27, 1.15–1.41), phenobarbital (PB; 1.79, 1.64–1.95), and valproate (VPA; 1.15, 1.05–1.26) were statistically significantly as-

sociated with risk of any fracture. Ethosuximide (0.75, 0.37–1.52), lamotrigine (1.04, 0.91–1.19), phenytoin (1.20, 1.00–1.43), primidone (1.18, 0.95–1.48), tiagabine (0.75, 0.40–1.41), topiramate (1.39, 0.99–1.96), and vigabatrin (0.93, 0.70–1.22) were not statistically significantly associated with fracture risk after adjustment for confounders. The relative increase was modest and in the same range for the significant and nonsignificant results. CBZ, PB, OXC, and VPA displayed a dose-response relation. Fracture risk was more increased by liver-inducing AEDs (OR, 1.38; 95% CI, 1.31–1.45) than by noninducing AEDs (1.19; 95% CI, 1.11–1.27).

*Conclusions:* A very limited increased fracture risk is present in users of CBZ, CZP, OXC, PB, and VPA. A limited significant increase cannot be excluded for the other AEDs because of the statistical power. **Key Words:** Epilepsy—Fracture—Risk—Antiepileptic drugs—Carbamazepine—Valproate—Phenobarbital.



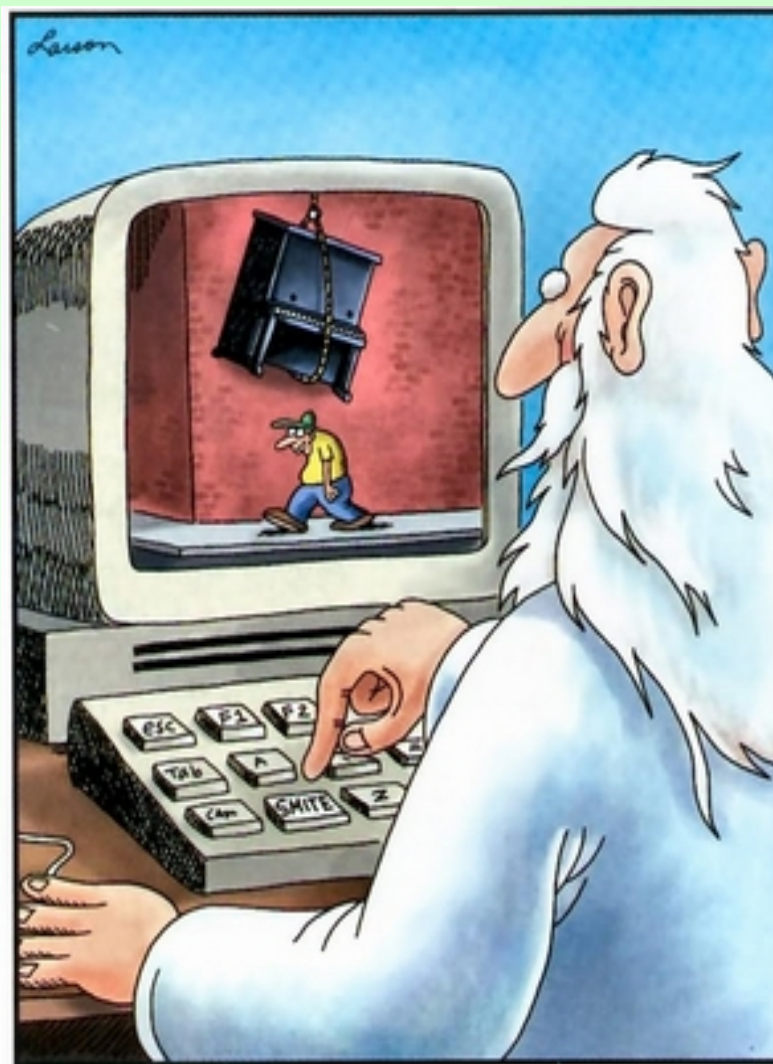
# Receptregistre, internationale

Navn, nation	Befolkningsgrundlag	Oprettet	Beskrivelse
GPRD, United Kingdom	3-4 mio	1987	Baseret på PC-administrativt system i almen praksis.
Pharmo, Holland	2,0 mio	1986	Baseret på apotekers kunderegistre. Kan kobles til indlæggelsesdata ved probabalistisk logik.
COMPASS / Medicaid, USA	Op til 8 mio	1977	Baseret på tilskudsordning til mindrebemidlede. Stor udskiftning af tilskudsberettigede (ca 25% per år). Dækningen er variabel.
Saskatchewan, Canada	1,0 mio	1989	Baseret på sygesikringsordning for Saskatchewan provinsen i Canada. Mulighed for kobling med indlæggelsesdata.
Nationalt norsk register	4,9 mio	2004	Ligner det danske. Ingen mulighed for kobling med diagnoser
Nationalt finsk register	5,2 mio	Ca 1993	Baseret på klausulerede tilskud. Høj dækning. Kan kobles med LPR
National svensk register	8,4 mio	2006	Mulighed for kobling til diagnoser
MEMO, Scotland	0,4 mio	1989	Alle recepter og diagnoser for Tayside befolkningen i Scotland.



# General Practitioners Research Database, GPRD

- Baseret på et PC-system til almen praksis
- Dækker alle udstedte recepter
- Har dækket 3-4 mio personer siden 1987
- >1500 praksis'er i UK. Ejes af UK Department of Health
- Detaljerede oplysninger om baseline variable; BMI, rygning, alkoholvaner etc.
- Dækker 90% af alle sygehus- eller ambulatoriebesøb
- Originale journaler er tilgængelige (\$\$\$)



God at His computer



## Farmakoepidemiologisk klinisk forsøg vs observationelt studie:

**Eksempel: er brug af mavesårsmedicin en årsag til benbrud?**

### **Klinisk forsøg:**

**Dobbelblindt forsøg, hvor en stor gruppe personer randomiseres til mavesårsmedicin eller placebo og følges over tid mht udvikling af benbrud...**

### **Observationelt studie**

**En stor gruppe personer kontaktes og udspørges om deres brug af mavesårsmedicin. Herefter følges de over tid, og incidensen af benbrud opgøres for brugere af mavesårsmedicin og for ikke-brugere.**



# Konfounding

**Usammenlignelighed...**

**Brugere af hjertemagnyl har flere hjertetilfælde end ikke-brugere...**

**Brugere af mavesårsmidler har flere maveblødninger end ikke-brugere...**

**Brugere af nye antidepressiva er oftere rygere end ikke-brugere...**

**Håndteres i design eller analyse**



## Registerbaserede bivirkningsstudier, forbehold

- Vekslede kvalitet af diagnosedata
- Uoplyste konfoundere (rygning, alkohol, vægt etc.)
- Manglende viden om håndkøbsmedicin
- (Usikkerhed om faktisk medicinindtagelse)



# Faglige miljøer:

## Dansk selskab for farmakoepidemiologi

- [www.farmakoepi.dk](http://www.farmakoepi.dk)
- Ca 100 medlemmer
- Udgiver nyhedsbrev
- Holder årsmøder og temamøder
- Formidler kontakter

## International Society of Pharmacoepidemiologi ISPE

- [www.pharmacoepi.org](http://www.pharmacoepi.org)
- To årlige kongresser. København, august 2008!
- Udgiver Pharmacoepidemiology and Drug Safety

## Diverse klinisk farmakologiske selskaber

- [www.dskf.org](http://www.dskf.org)



# Farmakoepidemiologi i Danmark, Status 2006

- Tre stærke faglige miljøer, København, Århus og Odense
- Flere store databaser med populationsdækning, gode muligheder for kobling til andre datakilder
- Internationalt konkurrencedygtige datakilder
- Stor offentlig interesse
- Begrænsninger i dækningen af databaser
- Usikkerhed om hvorvidt vi kan monitorere (og påvirke!) kvalitet af lægemiddelbrug