Pharmacoepidemiology an introduction

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Utrecht Institute for Pharmaceutical Sciences

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bridging molecule and patient environment

Pharmacoepidemiology & Clinical Pharmacology

Clinical Pharmacy

My personal mission

To describe, explain variation in
response to drugs (research)

Passion for unintended effects
Inspired by clinical puzzles

To predict response to drugs
for the individual patient
i.e. to reduce variability (care)

Today (13.00 – 16.30)

Occurrence relation
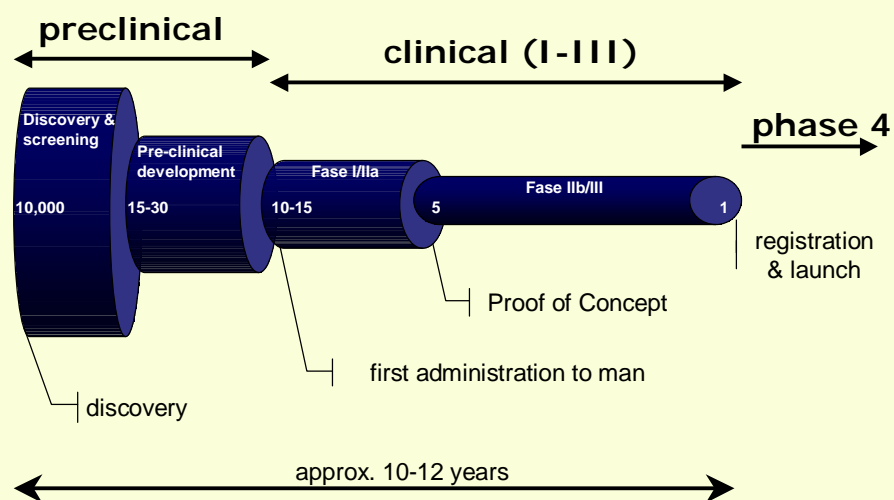
Hippocrates' domains

Study design – part 1

Lecture – group work – reflection
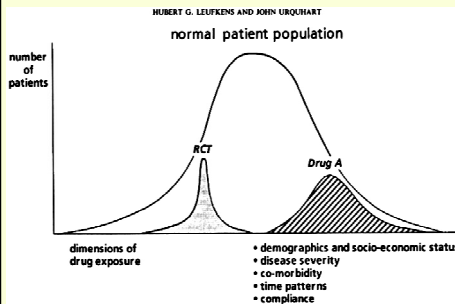*Study papers*
Design your study

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Why pharmacoepi in drug safety?

Drug evaluation never ends

preclinical

clinical (I-III)

phase 4

Discovery & screening

10,000

Pre-clinical development

15-30

Fase I/IIa

10-15

5

Fase IIb/III

1

registration & launch

Proof of Concept

first administration to man

discovery

approx. 10-12 years

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Slide 1

clinical trial   *clinical practice*

HUBERT G. LEUFKENS AND JOHN URQUHART

normal patient population

number of patients

RCT   Drug A

dimensions of drug exposure

- demographics and socio-economic status
- disease severity
- co-morbidity
- time patterns
- compliance

o **type of patients**

o **sample size**

o **duration**

o **type of questions**

o **way of observing**

Slide 2

People exposed to NCEs at the time of marketing
United Kingdom 1987-1989

	healthy volunteers	efficacy studies	safety database
all applications	68 (0-619)	861 (41-4906)	1171 (43-15962)
successful	92 (0-819)	1126 (122-4906)	1480 (129-9400)
unsuccessful	64 (0-431)	785 (41-4786)	1052 (43-15962)

Rawlins and Jefferys. BMJ 1991;302:223-5

What is probability of detection?

Side effect occurs 1 in 1000.
What evidence base (trials) is necessary to observe with 95% probability the side effect at least once?

Evidence base is 1500 patients.
Side effects with which incidence can be observed at least once with 95% probability?

By the way: what is....?

An adverse drug reaction / adverse effect

A side effect

An adverse event

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Definitions

Adverse Drug Event:
A harmful and unintended event occurring during drug therapy

Adverse Drug Reaction / Adverse Reaction:
A harmful and unintended event considered *related* **to drug therapy**

Side Effect:
An effect other than the intended one

Medication error

Side effects vs ADRs

Case Report   *Headache 1996;36:48*

Reduction of Migrainous Headaches During the Use of Acenocoumarol

E.P. van Puijenbroek, MD; A.C.G. Egberts; J.F.G. Trooster; J. Zomerdijk, MD

Not always bad news
Innovation trigger
e.g. sildenafil, thalidomide

Definitions

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Medication error

Hospital Admissions Related to Medication
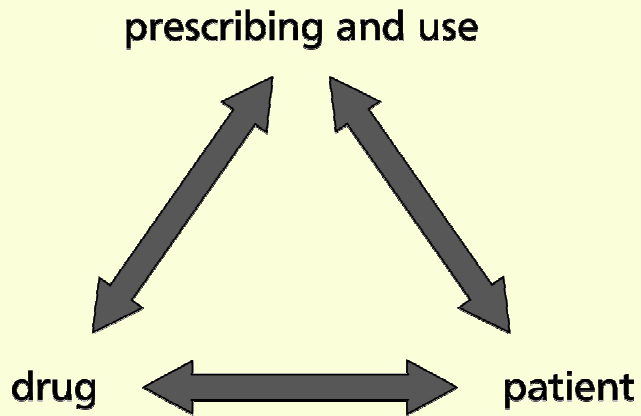# The HARM study

ORIGINAL INVESTIGATION

Frequency of and Risk Factors for Preventable
Medication-Related Hospital Admissions
in the Netherlands

Anne J. Leendertse, PharmD; Antoine C. G. Egberts, PhD; Lennart J. Stoker, PharmD;
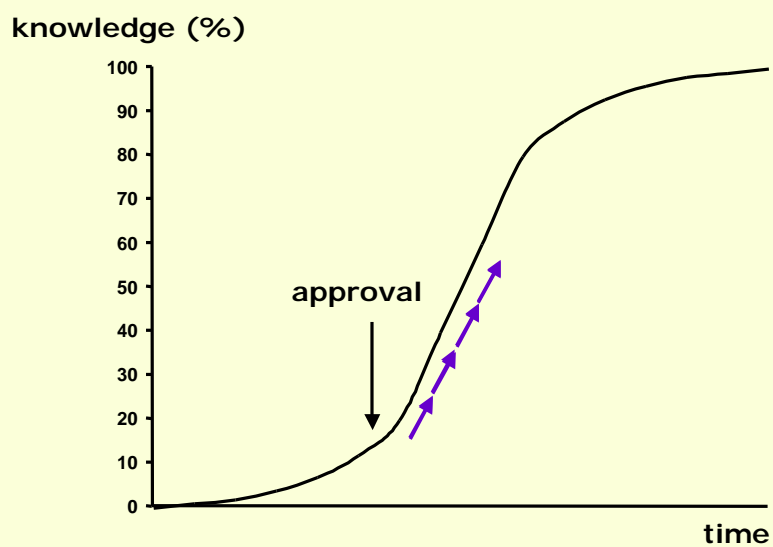Patricia M. L. A. van den Bemt, PhD; for the HARM Study Group

Results: Almost 13 000 unplanned admissions were screened, of which 714 (5.6%) were medication related. Almost half (46.5%) of these admissions were potentially preventable, resulting in 332 case patients matched

Arch Intern Med 23 september 2008

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Intrinsic vs extrinsic (un)safety

prescribing and use

drug ← → patient

The time-knowledge curve of NCEs

knowledge (%)

approval

time

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Epidemiology

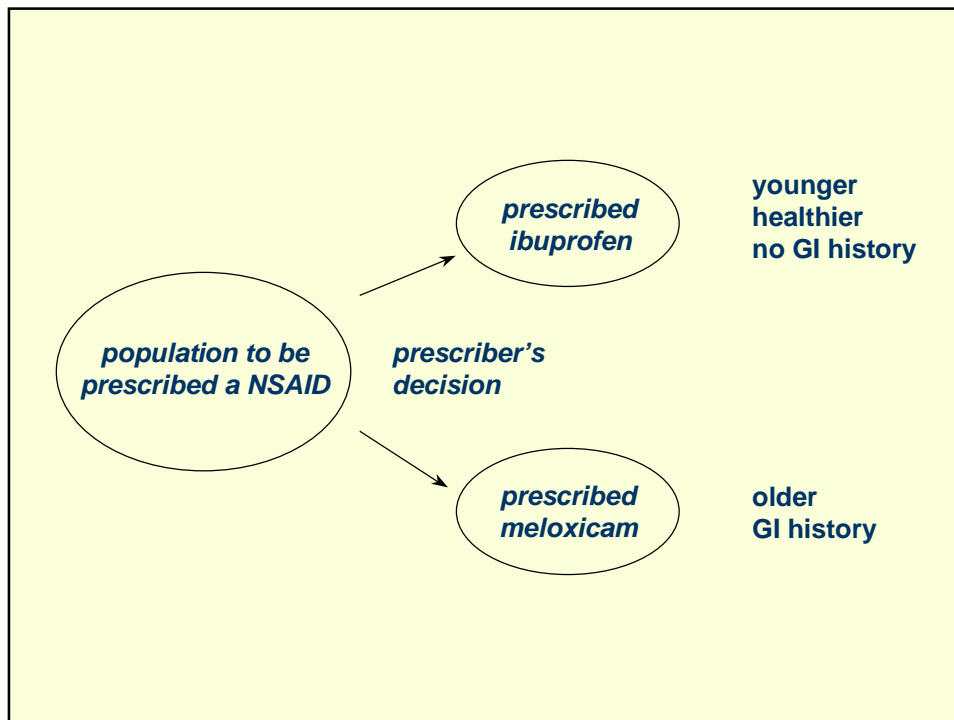Pr(outcome) = f(determinants)

Pharmacoepidemiology

-drug = outcome (drug utilization)

-drug = determinant (usually)

SSRIs - bleeds in orthopedic surgery

	serotonergic AD (n=26)	none (n=494)	P-value
Blood transfusion n (%)	6 (10%)	20 (4%)	<0.001
Perioperative blood loss	1019 ml	582 ml	0.001
Postoperative drainage	657 ml	495 ml	0.032

Arch Intern Med 2003;163:2354-8

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Selective prescribing of meloxicam

	meloxicam n=5000	ibuprofen n=5000
recent use NSAIDs	49.8%	7.9%
recent use H2 blockers	12.4%	4.0%
recent use proton-pump inh.	11.1%	4.0%
history of dyspepsia	38.4%	20.3%
history of peptic ulcer	6.1%	3.1%

Lanes et al. Pharmacoepidemiol & Drug Saf 2000;9:113-7
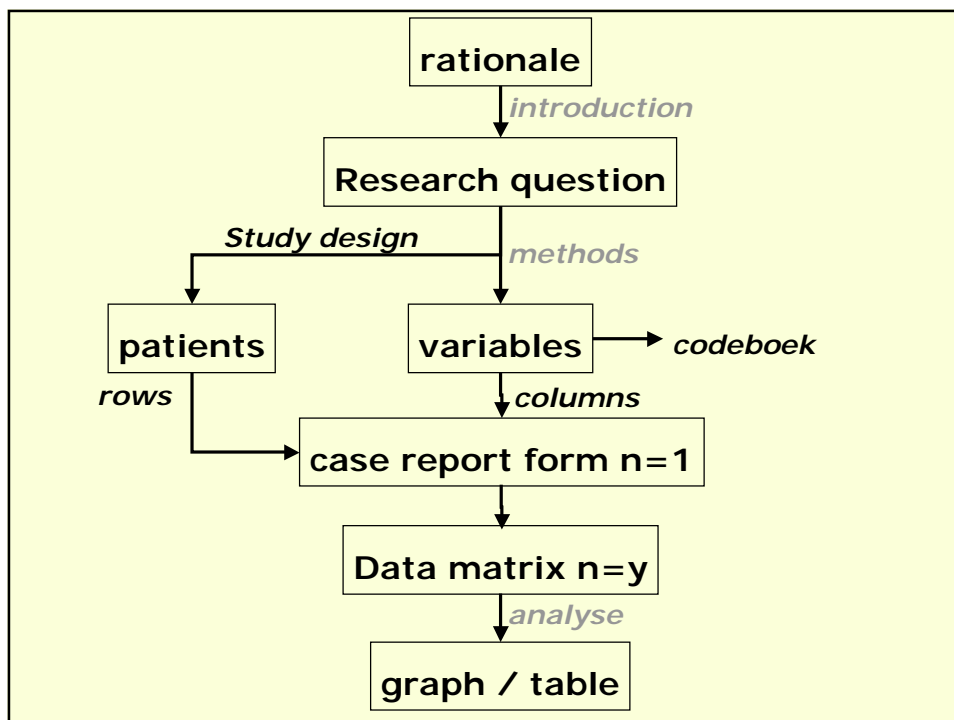
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Designing your research

Design (what)

-what do I want to know why?

-Objective and rationale

-Introduction section protocol / paper

Operationalize (how)

-        Patients: where (setting), who (in/exclusion), n

-Study design (I.e. trial, case control, follow-up)

-How to measure outcome, determinants, confounders

```
                    rationale
                        |
                        | introduction
                        v
               Research question
                        |
        Study design    | methods
          +-------------+
          v             v
      patients       variables  ---> codeboek
  rows    |             | columns
          +----> case report form n=1
                        |
                        v
                  Data matrix n=y
                        |
                        | analyse
                        v
                   graph / table
```

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Inspi-ration, transpi-ration, frust-ration

The occurrence relation

Determinant(s) ----------→ outcome(s)

characteristic/determinant	endpoint
exposure	disease
drugs	adverse effect
independent variable	dependent variable
The effect of....	on.....

Domain:

the population for which the occurrence relation

is of potential relevance

in....

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For comparison

P   patient

I   intervention

C   comparison

O   outcome

Key message

Consistency of the essential items occurrence relation in:

- Title
- Objective
- Methods
- Primary graph / table

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Assignment 1

Write down the occurrence relation of the papers

Determinant, outcome, domain

Write down your occurrence relation of interest

The objective of my study is to....

Draw most important graph/table