

Role of the physician and patient in more prudent and responsible medicine use.



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Question?

When drugs are released on the market it has been proven that they work.

- ▶ A. Right.
- ▶ B. Wrong.
- ▶ C. Do not know.

Question?

When drugs are released on the market it has been proven that they help patients.

- ▶ A. Right.
- ▶ B. Wrong.
- ▶ C. Do not know.

Topics.

- ▶ International Society of Drug Bulletins.
- ▶ Regulating authorities and pharmacovigilance centres.
- ▶ Efficacy and side effects.
- ▶ Efficacy of drugs? Two examples.
- ▶ How do people get better?
- ▶ Number Needed to Treat.
- ▶ Lessons to be learned.

- ▶ Not about emergency medicine, orphan drugs, new and expensive drugs.

International Society of Drug Bulletins (ISDB)

www.isdbweb.org/publications

European Commission



World Health Organisation

Drug and Therapeutic Bulletin, La Revue Prescrire, Buttlei
Groc, Arzneimittelbrief, Arznei-telegramm, Australian
Prescriber, Worst Pills Best Pills, Therapeutics Initiative

ISDB

- Promote rational prescribing.
- Discuss with the members of the European Parliament and the European regulating authorities to promote transparency concerning the registration procedures for new drugs.
- Actively exchange articles, discuss editorial procedures and promote their shared interests.

External contacts

- Consumer's organization.
- Pharmacovigilance Centers.
- Universities.
- Members of national and European Parliaments.
- Journalists and media.

What do we have?

We have a lot of good drugs that save lives and benefit patients:

- Antibiotics
- Painkillers
- Anesthetics
- Hormonal replacements
- Paracetamol

But there are also many exceptions.



Some data

- ▶ Drug costs € 5 billion each year in the Netherlands.
- ▶ More than 11 million drug users.

What is the scientific base of all this enormous amount of prescriptions and drug use?

What is the scientific evidence?



STATEMENT

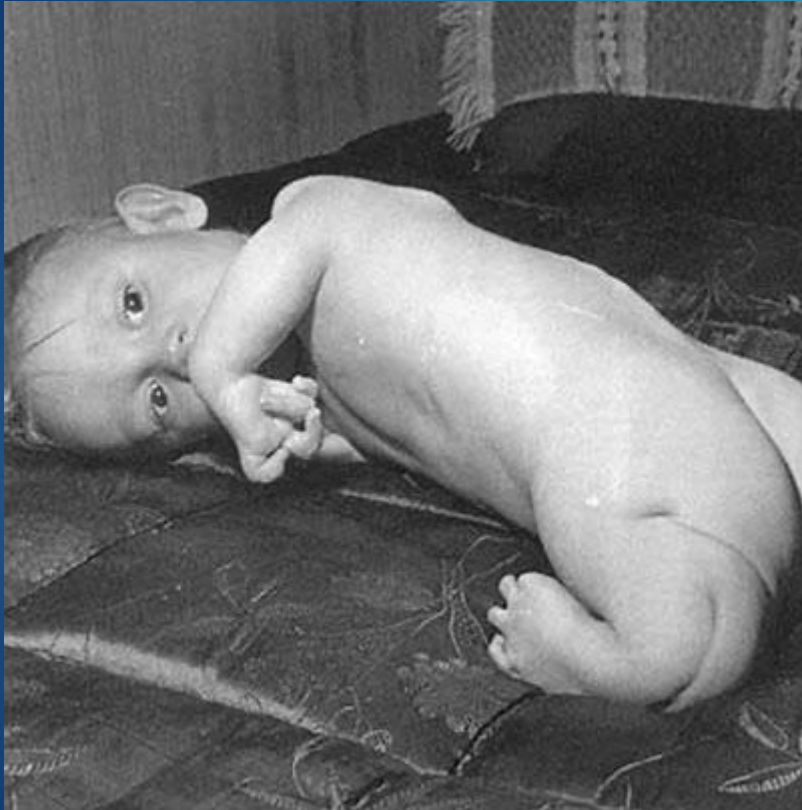
- After 22 years and reading some 25.000 studies on drugs I reached to the conclusion that:
- Most drugs don't work on individual patient-level.
- If they work they only work in a few patients and the balance of efficacy and safety is negative in most cases.

How did Bijl reach to these conclusions?

- ▶ Judgements based on rational pharmacotherapy.
- ▶ Doing science vs doing business.



Thalidomide (Softenon®).



Actions in Western countries.

- ▶ Regulating authorities.
- ▶ Pharmacovigilance centres for side-effects.

Softenon not in America.



JFK bestowing the Presidential Award for Distinguished Civilian Federal Service on Frances Kelsey



Market Authorisation

- ▶ Drugs can enter the market when the regulating authorities have concluded that the **balance of efficacy and side effects** is positive.
- ▶ European Medicines Agency **EMA**
- ▶ Bundesinstitut für Arzneimittel und Medizinprodukte:
BfArM and **Paul-Ehrlich-Institut**
- ▶ College ter Beoordeling van Geneesmiddelen **CBG**
- ▶ Food and Drug Administration **FDA**





Balance of efficacy and side effects.

- ▶ Very extensive studies.
- ▶ Pharmacodynamic and pharmacokinetic studies.
- ▶ Animal studies.
- ▶ Phase I studies
- ▶ Phase II
- ▶ Phase III
- ▶ Phase IV-studies.

- ▶ Market-authorization.

Central questions.

Efficacy: Do drugs work?

Side effects: are drugs safe for non-life threatening complaints and disorders?

On population level.



Efficacy.

- ▶ There are trials on animals etc.
- ▶ There is a (assumed pharmacologic) mode of action.
- ▶ There are receptors.
- ▶ **But...something has changed...**
- ▶ **Two examples: antidepressants and cancer drugs.**



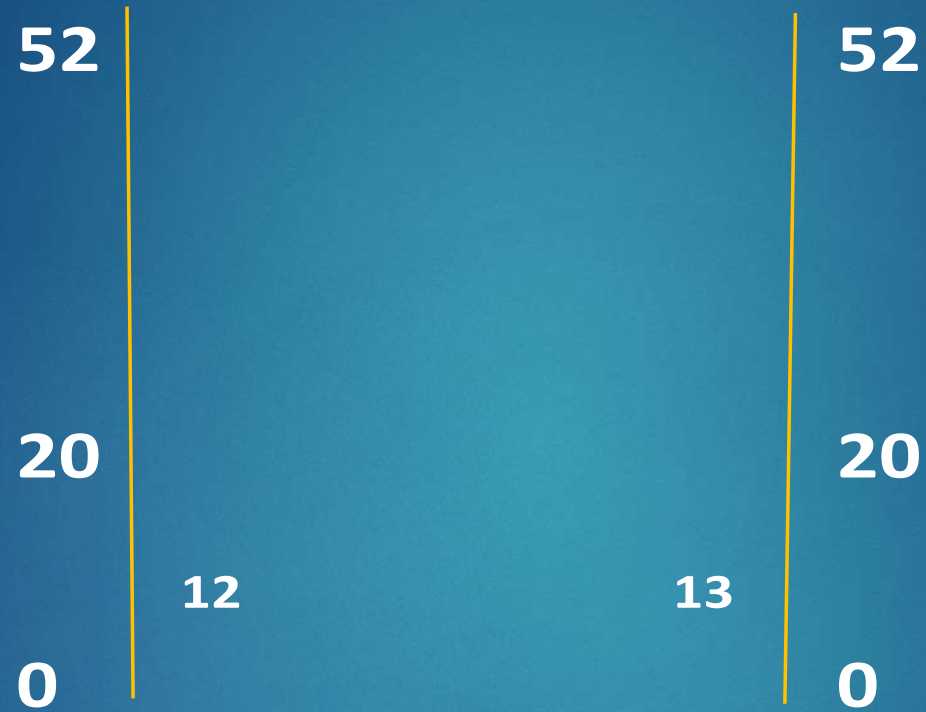
Antidepressants

- ▶ Measuring the severity of a depression.
- ▶ Hamilton Depression Rating Scale (HDRS or HAM-D).
- ▶ Scale 0 - 52.
- ▶ Severe depression ~ 20.



Anti- depressivum

Placebo



Vershil 1 punt op schaal van 52 punten is statistisch significant bij voldoende patiënten.

Klinisch relevant?

- ▶ A difference of 1 point on the HAM-D between an antidepressant and placebo is statistically significant.
- ▶ No doctor or patient can determine/ascertain such a difference, 3 is the minimum but 8 is substantial.
- ▶ But 1 point is enough (apart from many other data) to bring the drug to the market.



- ▶ So there is a change of the definition of 'efficacy' (mode of action) of a drug.
- ▶ Statistically significant is the aim, not whether patients feel and get better.
- ▶ If clinical relevance was demanded, no AD would have been granted a market-authorization.



Natural course of depression.

- ▶ 3 months: 1/3 are better.
- ▶ 6 months: 2/3 are better.
- ▶ When you use an antidepressant in these months you will assign the fact that you get better to the effect of the drug.
- ▶ But it is the natural course that you experience.
- ▶ No side effects.

Cancer drugs.

- ▶ For market authorization a statistically significant effect on tumor volume or time to progression of the cancer is enough.
- ▶ But for patients is relevant: do I live longer (**general survival**) and in what shape do I live these extra days, weeks or months (**quality of life**)?
- ▶ Manufacturers do not have to show effects on these clinical relevant measures.

Cancer drugs.

- ▶ Manufacturers do not have to show effects on these clinical relevant measures of general survival and quality of life.
- ▶ Actually, in most cases there are no effects on these endpoints. In a minority of trials general survival increases with a few weeks up to 2 months. But, at the cost of what?



Other examples.

- ▶ **Antipsychotics.**
- ▶ Psychosis symptom ranking: PANSS 0-210.
- ▶ Statistically significant is 6 points difference but clinical relevant is at least 15 points.
- ▶ **Many more examples: drugs against dementia, antidiabetic drugs, sleeping pills, weight losing pills, etc etc.**



Conclusion on efficacy.

- ▶ Manufacturers have made a new definition of 'efficacy': drugs work when they exert a mathematical effect, a statistically significant effect.
- ▶ Most patients do not experience that drugs help them, there is no clinical relevant effect.
- ▶ They get better anyway.



Treatment effect.

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$$OE = SE + NC + EV + ME.$$

WE = observed effect.

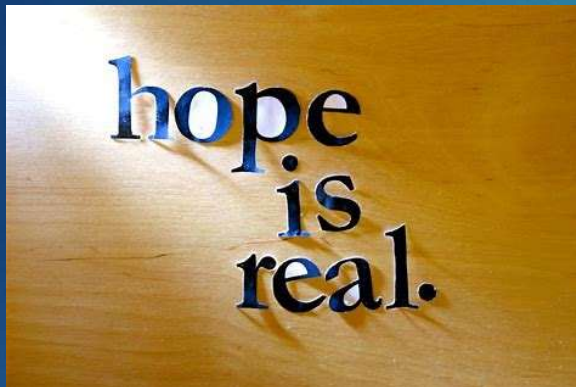
SE = specific (pharmacologic) effect.

NB = natural course of the disease.

EV = external variables (confounding, bias, **hope and expectations**, placebo-effect).

MF = measurement errors.

Hope and expectation.



NC and EV: How do patients feel relief and get better?

- ▶ Natural course of diseases
- ▶ Regression to the mean or 'the friend of the doctor'
- ▶ Placebo-effects
- ▶ Empathy.

Natural cause of complaints and diseases

In **most guidelines** both in primary (and in some cases secondary) care first choice is a non-drug therapy. Why?

- In general practice most complaints resolve spontaneously.
- The natural cause of most complaints and diseases is positive and self-limiting.
- There are (hardly) no side-effects.

Drug safety.



- ▶ Medicines are one of the most important causes of death.
- ▶ Third leading cause of death according to some, after cardiovascular diseases and cancer.
- ▶ In the EU every year more than 200. 000 people die because of the use of drugs.

Drug **safety**: examples of failures of the regulating authorities

- ▶ Rofecoxib (Vioxx) >100.000 deaths
- ▶ Celecoxib hundreds
- ▶ Diclofenac hundreds
- ▶ Rosiglitazon (Avandia) 47.000 deaths
- ▶ Mediator (France only) 500 – 2.000 deaths

NNT

- NNT is the **number** of patients that **need to be treated** with a drug during a certain time to prevent a particular incident (e.g. myocardial infarction, stroke or relapse of depression).
- NNT 50 means that 50 patients have to be treated with a drug to prevent one incident in one person. Therefore in 49 patients there is no effect but there are side-effects.

NNT's of common diseases based on **best evidence** provided by the Cochrane Collaboration

- Functional dyspepsia PPI's NNT 13.
- Episodic tension-type headache paracetamol NNT 22.
- Mortality in hypertension: unclear.
- Prevention of sudden death in hypertension: no effect. Yet NNT 333 non-fatal MI and NNT 333 fatal MI.

NNT's of common diseases based on **best evidence provided by the Cochrane Collaboration**

- Pain reduction after antibiotics for acute middle ear infection in children NNT 20.
- Omega-3-fatty acids for primary prevention of CVD NNT unknown.

The interplay between the pharmaceutical industry and the regulating authorities.

- ▶ Doing business vs doing science.
- ▶ Conflicts of interest.
- ▶ Transparency.



Lessons to be learned.

- ▶ More attention for the safety of patients.
- ▶ Would you accept that so many patients (or your family) die because of inappropriate evaluated drugs?
- ▶ And what if you knew that most of these drugs are used for non-life threatening diseases or complaints?

Patients

- ▶ More attention to non-drug interventions.
- ▶ What do I expect from the doctor: a prescription, an advice, a diagnosis, reassurance?
- ▶ Advices: Stop smoking
Promote exercise
Healthier diet. } **life-style
medicine**

Physicians

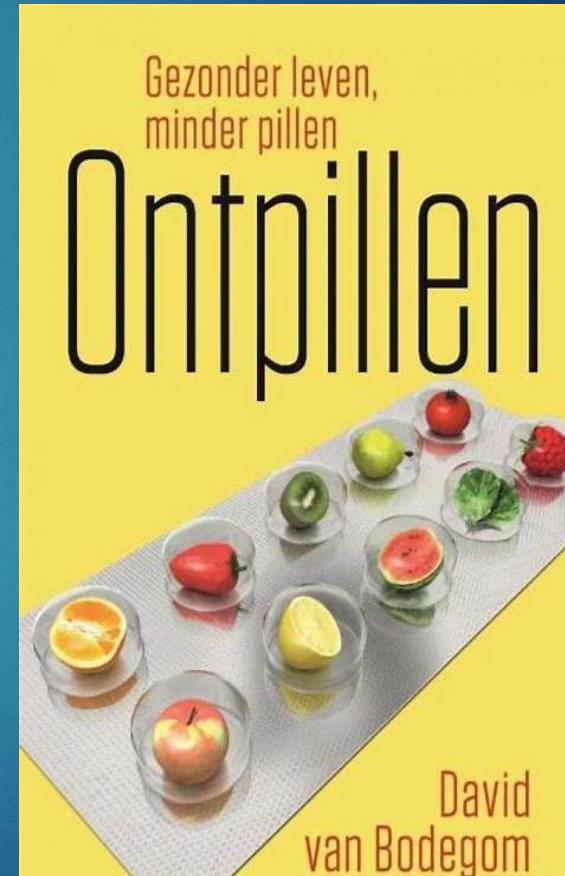
- ▶ More attention for non-drug interventions.
- ▶ Promote healthier way of living: life-style medicine
- ▶ Start with low-dose, short-term, easy and cheap drugs.

- ▶ Remember :- Placebo-effects
 - Regression to the mean
 - Natural course of diseases
 - Empathy.

Why most drugs
don't work and
don't help patients.



De-prescribe.
Entpillen?
Weniger schlucken



Conclusions.

- ▶ The majority of drugs are not licensed because they cure or heal patients but because the manufacturer has shown that the drug performs mathematically (statistically significant) better than placebo. **Doing business.**
- ▶ But not clinical relevant better. And not in the best interest of patients. **Doing science.**
- ▶ Natural course of diseases is good in most cases.
- ▶ Non-drug therapies are preferred.
- ▶ De-prescribe.
- ▶ Life-style medicine.

