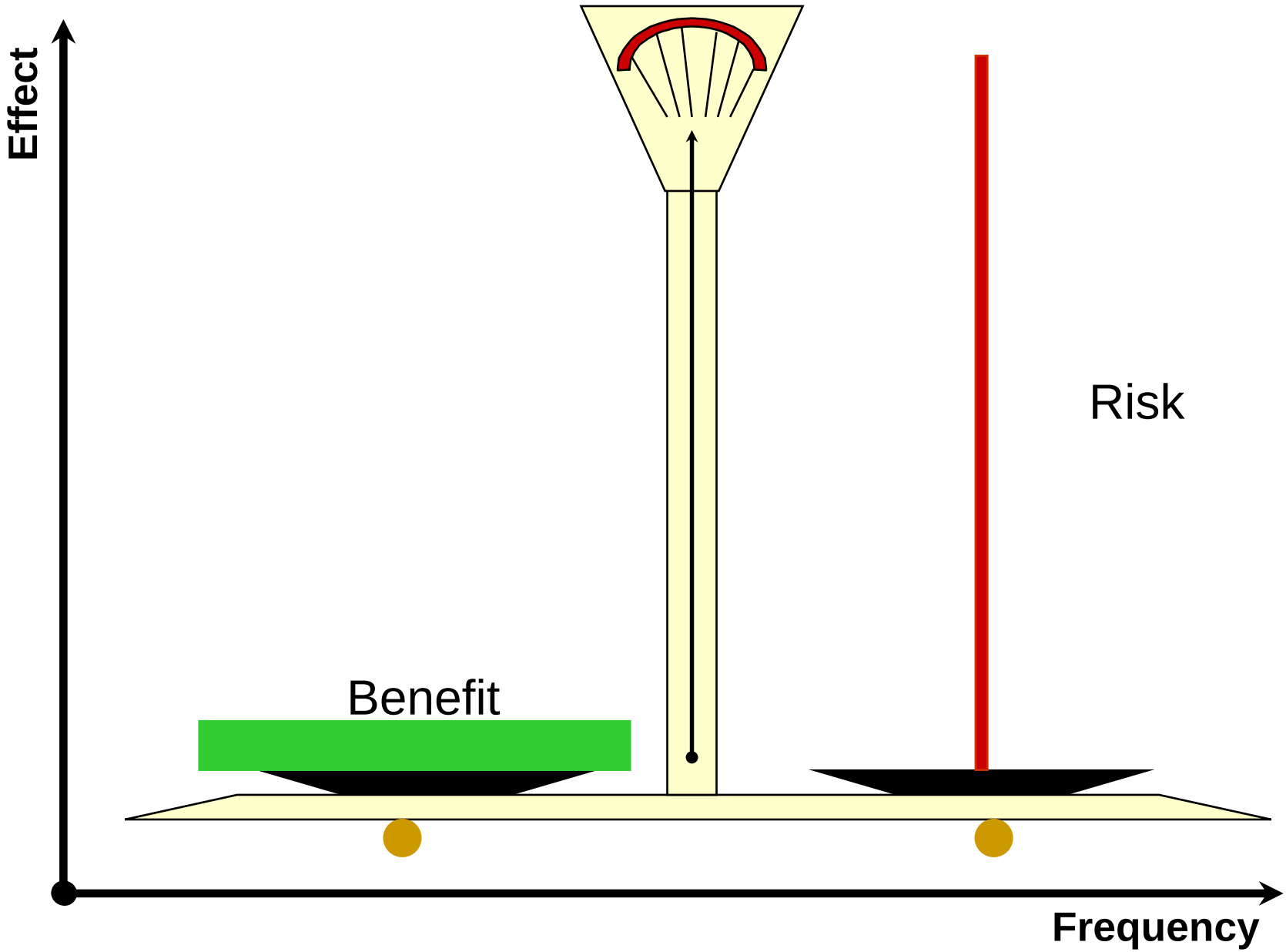
Comparing Therapeutic Benefit and Risk

RHB Meyboom, ACG Egberts

Thérapie 1999;54:29-34

The weight is the same but the “pressure” is not



- **Can benefit and risk be measured in one and the same standard unit?**

- **Will such calculations present the dilemma that ‘a drug causes benefit in many at the cost of serious injury in some’ in an understandable way?**

- **Clinical trials (type A adverse effects)**
- **Spontaneous reporting (detection)**
- **Prescription Event Monitoring**

➢ **Selected patients**

  – **Hospital studies**

➢ **Selected diseases**

  – **Case control surveillance**

➢ **Selected drugs**

  – **Follow-up studies**

Selected patients
Causes of Hospital Admission

Drug-related problems	**16.2%**
Therapeutic failure	**54.8%**
Adverse reactions	**32.9%**
Overdose	**12.3%**

Nelson KM, Talbert RL. Pharmacotherapy 1996;16:701-7

Causes of Hospital Admission

Nelson KM, Talbert RL. Pharmacotherapy 1996;16:701-7

Agents implicated	%
• Hypoglycemic	15.8
• Diuretic	10
• Antiinfective	9
• Cardiovascular	8
• Psychotropic	7
• Gastrointestinal	7
• NSAIDs, aspirin	4
• Anticonvulsants	2
• Steroids	2
• Antineoplastic	2

Limitations

- **Frequently used drugs**
- **Frequent adverse effects**
- **Drug groups**

Selected diseases	Incidence/ year/10^5	Drug fraction %
• Lyell syndrome	0.04-0.12	80
• Aplastic anaemia	0.2	20
• Agranulocytosis	0.35	70
• Stevens Johnson	0.12-0.6	50
• Anaphylaxis	1	45
• Uraemia chronic	10	10
• GI haemorrhage	50	50
• Pancreatitis acute	50-150	< 10
• Traffic accidents (admissions)	77	2.6
• Falls (treated)	2700	7
• Asthma	5000	10

Case control surveillance

- Epidemiology of disease
  - Incidence
  - Clinical, course, outcome
  - Causes (all)
  - Drug fraction
  - Individual drugs
- Expensive; funding?
  - Few adverse reactions studied

Selected drugs
Follow-up studies

- Quantitative information (numerator and denominator)
- High quality of data

- Mainly common and serious diseases with established treatment protocols
- Large cohort needed for rare reactions
- Funding?

Selected drugs
Follow-up studies

- Antidiabetics
- Antithyroids
- Antirheumatics (DMARDs)
- Anticonvulsants
- Antiarrythmics
- Anticoagulants
- Oncolytics
- Antiretroviral

Knowledge of an adverse effect

- **Pieces of information of different source and nature**
- **May be ambiguous or inconsistent**
- **Incomplete**

Cumulative risk of death associated with fertility control methods (per 10^5 women)

Method	Age groups			Total
	15-34	35-39	40-44	15-44
Condom & abortion	1	<1	<1	1
Condom	19	2	2	23
Pill (non-smokers)	21	70	160	251
IUD	25	10	10	45
Abortion	26	9	6	41
Diaphragm /spermicide	28	11	14	53
Rhythm	36	14	18	68
Pill/smokers	132	257	588	977
No method	192	129	141	462

Lebech PE, Ottesen B. Side Effects of Drugs Annual 8, 1984

The benefit of a drug can be expressed as the Drug Attributed Gain of Quality-Adjusted Life Years (DAGQALY)

The cumulative risk of a drug can be calculated as the Drug-Attributed Loss of Quality-Adjusted Life Years (DALQALY)

Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Report of CIOMS Working Group IV. Council for International Organizations of Medical Sciences, Avenue Appia, 1211 Geneva 27, Switzerland, 1998.

The 'Principle of Threes'

Simplification of the total adverse effects profile of a drug by considering:

- the 3 most common adverse effects, and

- the 3 most serious adverse effects

Gradation:	**high = 3**	**medium = 2**	**low = 1**
Seriousness:	**fatal**	**disabling**	**inconvenient**
Duration:	**permanent**	**persistent**	**temporary**
Incidence:	**common**	**frequent**	**rare**

IR Edwards, BE Wiholm, C Martinez. Drug Safety 1996;1-7

The 'Principle of Threes'

	Gradation		
	High	Medium	Low
Disease (indication)			
Seriousness			
Duration			
Incidence			
Improvement produced by the drug			
Seriousness (level)			
Duration			
Incidence			
Adverse effects of the drug			
Seriousness			
Duration			
Incidence			

Most approved drugs have a favorable benefit-risk balance, if taken appropriately

- **Right indication**
- **Right dose**
- **Right precautions**
- **Right expectations**

Causes of Hospital Admission

Drug-related problems	**16.2%**
Therapeutic failure	**54.8%**
Adverse reactions	**32.9%**
Overdose	**12.3%**
⇒ Avoidable	**49.3%**

Nelson KM, Talbert RL. Pharmacotherapy 1996;16:701-7

The safety of a drug is not a constant and absolute feature. It is influenced by the conditions of use:

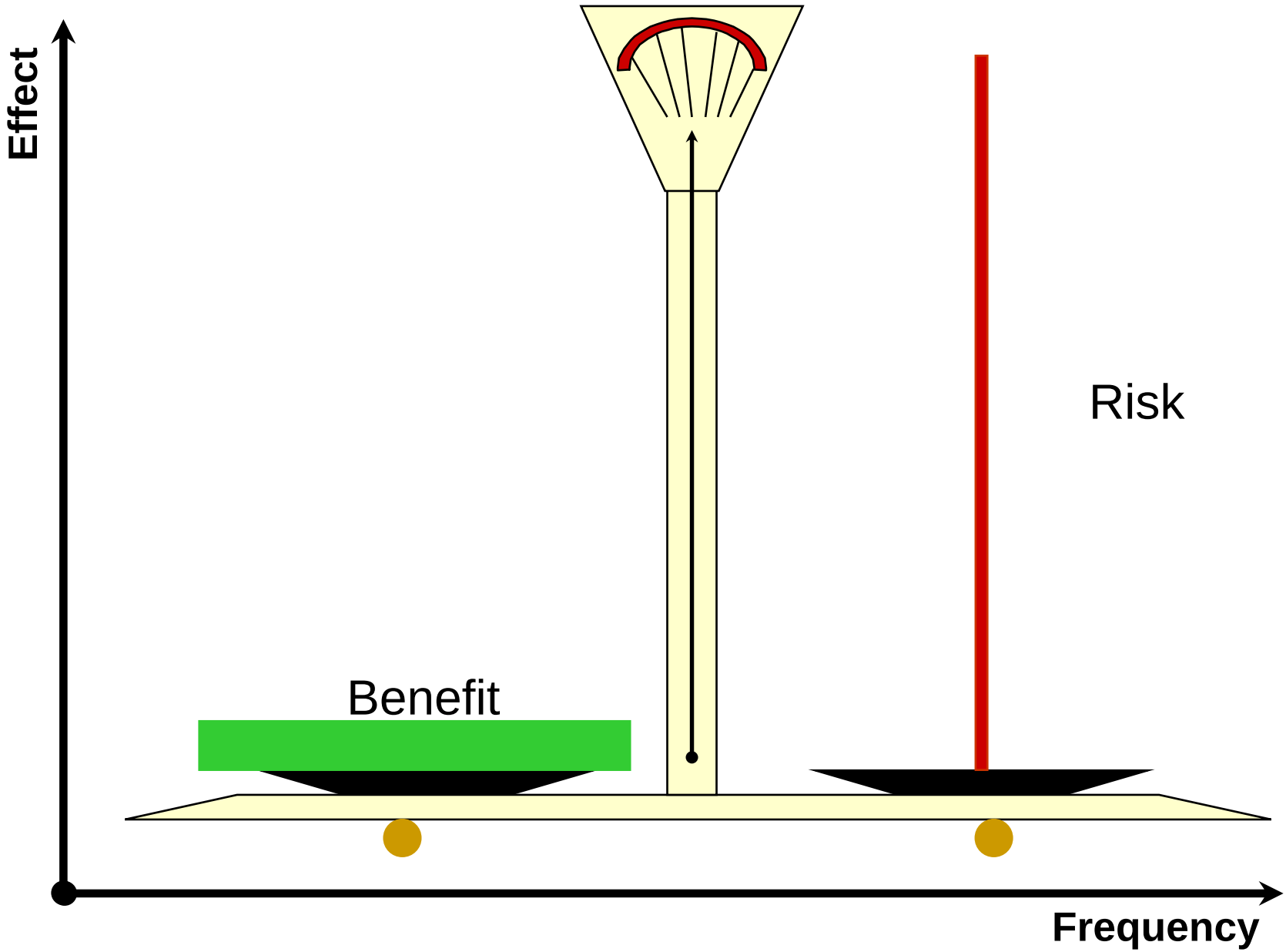
- **Patient information and counseling**
- **Therapeutic monitoring**
- **(Non)compliance**
- **Expectations, attitude & lifestyle**
- **Genetic factors**
- **Environmental factors**
- **Medication error**

- **Benefit–harm assessment is meaningful in a given context, e.g.:**
  - **indication**
  - **individual treatment decisions**
  - **drug comparisons**
  - **drug policy (regional, national)**
  - **public health**
  - **pharmacoeconomics**

- **For many medicines there is not enough information for an exact measurement of benefit and harm**
- **It is not (yet) possible to calculate the balance of benefit and harm in one ‘merit unit’**
- **A *meta analysis* is a promising practical approach**

The seriousness of an adverse reaction should not be disproportionate to that of the disorder treated

The weight is the same but the “pressure” is not



Better benefit-harm assessment will improve rational drug use, but there is still much to be done

- Comprehensive data collection (computerised medical and pharmaceutical practices)
- Education of physicians, pharmacists and other health care professionals
- Transparency and realism of the information to patients and prescribers (‘good communications practice’)
- Improvement of health education in general
- Control of drug promotion

Better benefit-harm assessment will improve rational drug use, but there is still much to be done

- **"Nonsteroidal antiinflammatory drugs should be avoided when possible; when they are used the lowest effective dose of the least toxic drug should be used for the shortest period possible"**

  MacDonald et al. Brit Med Journal 1997;315:1333-7

- **However, these drugs are still heavily promoted, heavily prescribed, available for self-medication and heavily used**

Underreporting

Developed systems:

- **Reporting rate > 250/10^6/year**
- **10% of physicians / year**
- **Reporting range of serious reactions ca. 4 - 30%**

The degree of underreporting is:

- **unknown**
- **often large**
- **variable**

Adjusting for underreporting is difficult

Consequences of underreporting

Decreased reliability of the system:

- Delay in signal detection (small monitored population)
- No quantitative estimation; comparison of drugs difficult
- The system cannot demonstrate safety

Decreased credibility of the centre and of drug regulation

Why practitioners do not report (Inman's 'seven deadly sins', 1978):

- Complacency ('approved drugs are safe')
- Fear (for litigation)
- Guilt ('first of all do no harm')
- Ambition (to publish)
- Ignorance
- Diffidence (about reporting suspicions)
- Lethargy (too busy)

UMC Study

Biriell C, Edwards IR. Pharmacoepidemiology and Drug Safety 1997;6:21-6

- **Complex time-consuming forms**
- **Lack of feedback or encouragement**
- **Pressure of time**
- **Requests or fear of requests for further information**

Why or when practitioners do report:

Biriell C, Edwards IR. Pharmacoepidemiology and Drug Safety 1997;6:21-6

- **A positive relationship between the Pharmacovigilance Centre and the reporter**
- **Active personal and general feed-back and encouragement from the Centre**
- **Simple and readily available report forms**
- **Motivation to contribute to medical knowledge**
- **Unusual or unknown adverse reaction**
- **New drug**
- **Severity or seriousness of the adverse reaction**
- **Strong suspicion of a causal relationship; plausible time relationship**
- **Known association between drug and reaction**

- **Active and encouraging promotion of the benefits of ADR reporting**
- **Give consideration to the needs of particular professional groups in promotional activities**
- **Focusing attention on new drugs, observed possible ADRs, and on the most important categories of reactions**
- **Develop clear criteria for the recognition of events that need prompt reporting**
- **Simple accessible forms (or systems) for reporting and follow-up**
- **Personal encouragement, recognition and feed-back for reporters**
- **Produce evidence of the usefulness of reporting (publications, bulletins, notified regulatory decisions, etc.)**