Measuring drug exposure: rationale and methods

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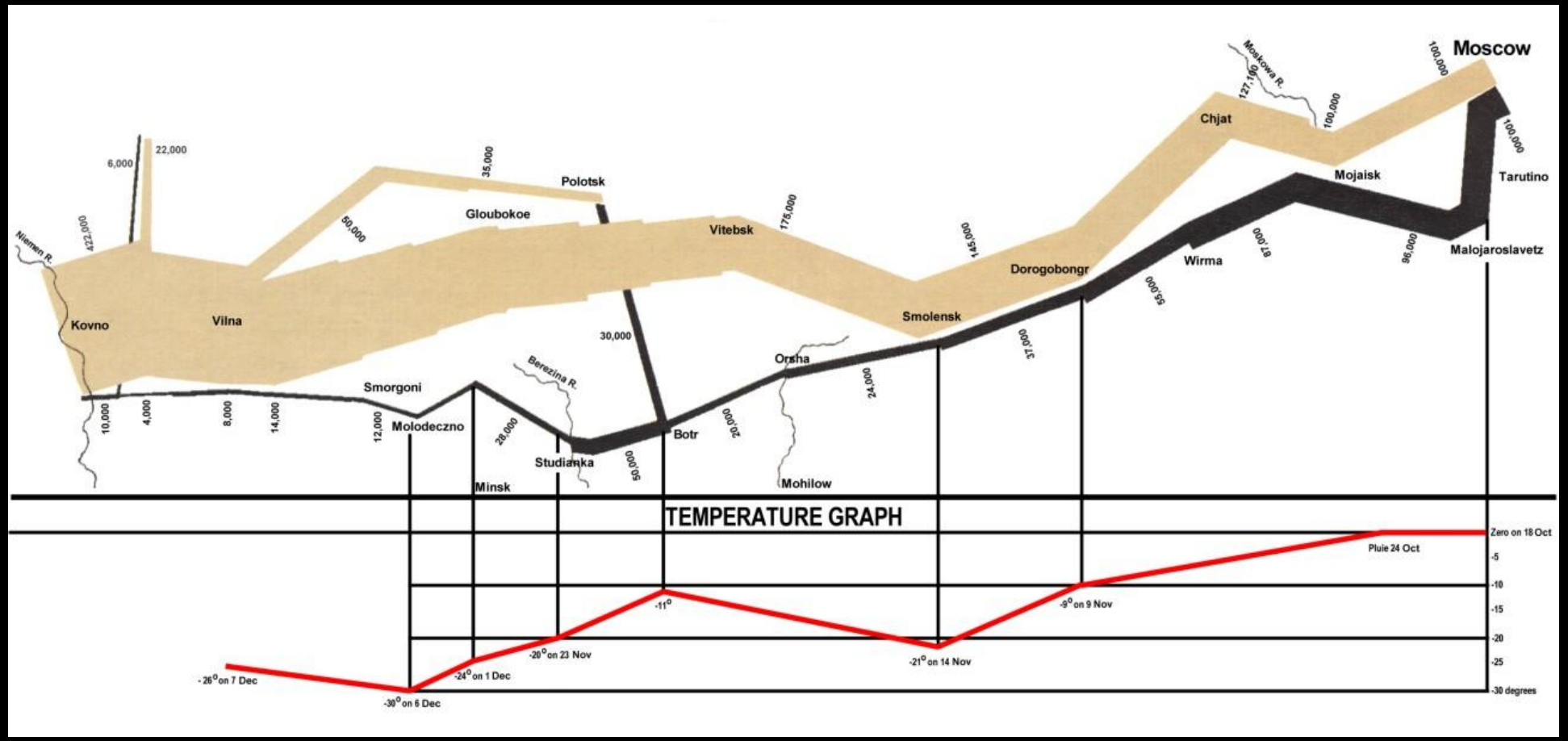
Declaration of interests

- Chairman of the Dutch Medicines Evaluation Board (MEB), since mid 2007.
- Professor of Pharmacoepidemiology, Utrecht Institute of Pharmaceutical Sciences, 0.4 FTE.
- Co-opted member of CHMP PhVWP, since 2006.
- This talk reflects my personal views; I am being inspired and challenged on a daily basis by many colleagues from these ‘environments’.

Napoleon's 1812-1813 March on Moscow: exposure and outcomes



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HRT 'can shrink women's brains', claims new study

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NEUROLOGY 2009;72:135-142

Postmenopausal hormone therapy and regional brain volumes

The WHIMS-MRI Study

S. M. Resnick, PhD, M. A. Espeland, PhD, S. A. Jaramillo, MS, C. Hirsch, MD, M. L. Stefanick, PhD, A. M. Murray, MD, MSc, J. Ockene, PhD Med, C. Davatzikos, PhD For the Women's Health Initiative Memory Study*

Trust in the financial system has been badly shaken

Exposure assessment is not a yes/no question

Examples:

Drug induced nephrotoxity
ICS and fracture risk

Table 1. Cases of drug-induced nephrotoxicity and their pharmacovigilance commonalities

	Signal factors	Exposure factors	Denominator data	Confounding factors, effect modifiers
Phenacetin	Spontaneous reports, time gap signal and use	OTC, combined with other analgesics	Poor	Co-medications, disease severity, protopatic bias
Protease inhibitors	Already known from RCTs	Combined with other drugs, dosing	Good quality, large cohorts	Previous treatment, body mass, climate
Statins	Spontaneous reports, public media effects	Shift to high potency use, class effect?	Good quality	Drug channelling, selective prescribing
Contrast agents	Problem not signalled by prescriber/radiologist	Timing of exposure, class effect?	Poor	Co-morbidity, confounding by marketing
Cyclosporine	Already known from RCTs	Dose/duration of use, long-term effects	Reasonable quality	Confounding by renal transplant indication

Leufkens HG, Egberts AC. Pharmacovigilance: from signal to action. In: Broe ME de, Porter GA, eds. Clincal Nephrotoxins. 3rd Ed, 2008: 90.

Inhaled steroids and bone density

INHALED CORTICOSTEROIDS AND HIP FRACTURE: DISEASE OR DRUGS?

To the Editor:

Hubbard and colleagues report a study using the General Practice Research Database exploring the relationship between inhaled corticosteroids and the risk of hip fracture. In so doing, they replicate findings recently presented by our own group, but fail to interpret these with due care (1). Using the traditional epidemiological cohort study design, we identified all users of inhaled corticosteroids, and identified fracture incidence among them (2). We contrasted incidence rates with cohorts who used inhaled bronchodilator therapy, but did not use inhaled corticosteroids, and with a control cohort who were matched by age and sex to the inhaled corticosteroids users, but did not suffer from asthma. In contrast, Hubbard and colleagues commenced with the fractures and looked back at exposure history using a nested case–control design. The difference in methodology represents different types of sampling, and should give identical results if derived from the same population (3). The two studies did indeed produce almost identical results with respect to the relative rate of hip fracture in inhaled corticosteroid users, but varied in the evaluation of the role of the underlying disease.

To ascribe the effect of inhaled corticosteroid use to the drug, as compared with the disease or its comorbid correlates, seems to us erroneous. The key finding of our study was that an increased risk of fracture was also observed when patients using noncorticosteroid bronchodilator drugs were compared with controls. The risks associated with noncorticosteroid bronchodi-

KL, Greenland S, editors. Modern
Lippincott-Raven Publishers; 1998

From the Authors:

We thank Dr. van Staa and colle
paper, but a number of their con

Our two studies differ with r
control group (1, 2). We choose
study, with controls sampled fro
dian follow-up time 2.7 years). va
cohorts exposed to inhaled cortic
tors but not inhaled corticosteroi
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0.9, 0.2, and 2.3 years, respective

The main question we addre
inhaled corticosteroids was assoc
so, was this explained by other
corticosteroids. We examined an
founders including all corticoste
diagnoses, and all other drug exp
than that examined by van Staa
hip fracture, van Staa and colleag
prescribed inhaled corticosteroi
fracture and whether this was exp
ease, hence the need for two cont
were similar regardless of which
rate ratios for hip fracture were
[CI], 1.04 to 1.43) with unexpose
0.99 to 1.45) with bronchodilator

Correspondence

Bone Loss and Inhaled Glucocorticoids

To the Editor: The study by Israel et al. (Sept. 27 issue)[1] of bone thinning in women with asthma did not effectively control for the critical variables of the level of physical activity and the severity of asthma.

Comparisons between patients with mild asthma and those with persistent asthma who are receiving high doses of inhaled glucocorticoids must include a careful evaluation of base-line characteristics.[2] Table 2 of the article shows that the 28 women who did not use inhaled glucocorticoids weighed less than the 42 women who required more than eight puffs of inhaled glucocorticoids per day (mean [±SD], 140±20 vs. 154±40 lb), had nearly twice the level of phys-

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van Staa TP, Leufkens H, Cooper C. N Engl J Med 2002; 346: 533-4.
van Staa TP, Leufkens H, Cooper C. Am J Respir Crit Care Med 2003;168: 128.

Inhaled steroid induced fracture risk and dose

beclomethasone equivalents	Low dose < 300 μg/day	Medium dose 300-700 μg /day	High dose >700 μg /day
	(N=46,797)	(N=43,070)	(N=28,815)
Non-vertebral	1.11 (1.03-1.20)	1.16 (1.07-1.26)	1.28 (1.15-1.42)
Forearm	1.06 (0.90-1.24)	1.19 (1.00- 1.41)	1.15 (0.94-1.42)
Hip	0.95 (0.67-1.34)	1.06 (0.80-1.40)	1.77 (1.31-2.40)
Vertebral	1.31 (0.89-1.92)	1.39 (0.95-2.04)	2.50 (1.63-3.83)

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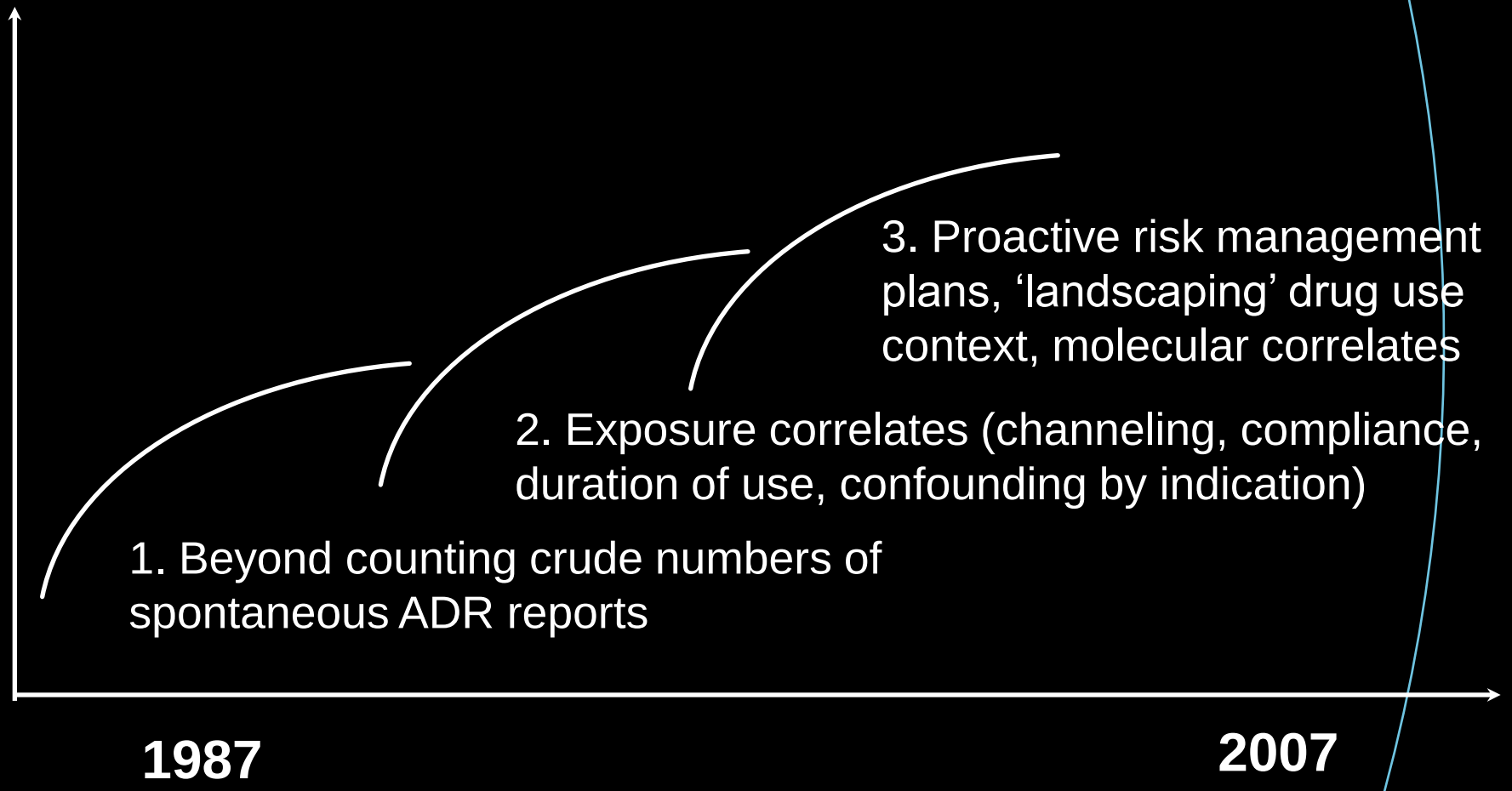
Staa TP van, Leufkens HGM et al, J Bone Miner Res 2001;16: 581-8.

Two decades of progress in drug safety assessment-management: three phases

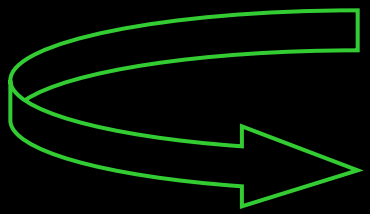


Regulatory drug exposure issues (who is using what, when, how long, at what dosages)

Exposure	Outcome	Example
Pregnancy exposure (in different phases)	Congenital abnormalities	Lamotrigine, ACE-inhibitors, SSRIs
Strong increase of use over time	Stroke, other CV effects	Methylphenidate
Drug exposure as part diagnostic procedure	Nephrogenic Systemic Fibrosis (NSF)	Gadolinium products in MR radiology
Long-term use	Several	Biphosponates, biologicals, statins
Acute, single dose, in crisis situation	Several	Pandemic influenza vaccines
Contaminated product	Several	Ethyl mesylate in Nelfinavir (Viracept)

Measures of drug exposure

- Incidence of use: ‘start of therapy at a certain moment in the time window of observation’
- Prevalence of use: ‘exposed at a certain moment (or period) in the time window of observation’ (for chronic therapy the DDD/1000 p/day is a good surrogate estimate of the prevalence when the PDD/DDD equals 1)
- Person-time of use: ‘accumulated units of time (days, years) with ascertained exposure’
- Exposure profile



variable drug exposure patterns drive to case-control studies

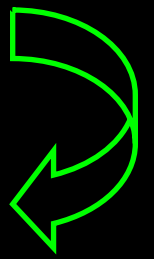
Reliability of drug exposure data

Evaluate the sequence of:

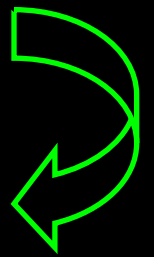
prescribing

dispensing

actual use



Primary drug defaulting



Patient non-compliance

Cave:

- Self medication, OTC
- Drug prescribing/ dispensing by nurses, other health professionals
- Biologicals, vaccins, etc. through special programs

Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

Thijs J. Giezen, PharmD
Aukje K. Mantel-Teeuwisse, PhD
Sabine M. J. M. Straus, MD, PhD
Huub Schellekens, PhD
Hubert G. M. Leufkens, PhD
Antoine C. G. Egberts, PhD

Context Biologicals are a relatively new class of medicines that carry specific risks (eg, immunogenicity). However, limited information is available on the nature and timing of safety problems with their use that were identified after approval.

Objective To determine the nature, frequency, and timing of safety-related regulatory actions for biologicals following approval in the United States and/or the European Union.

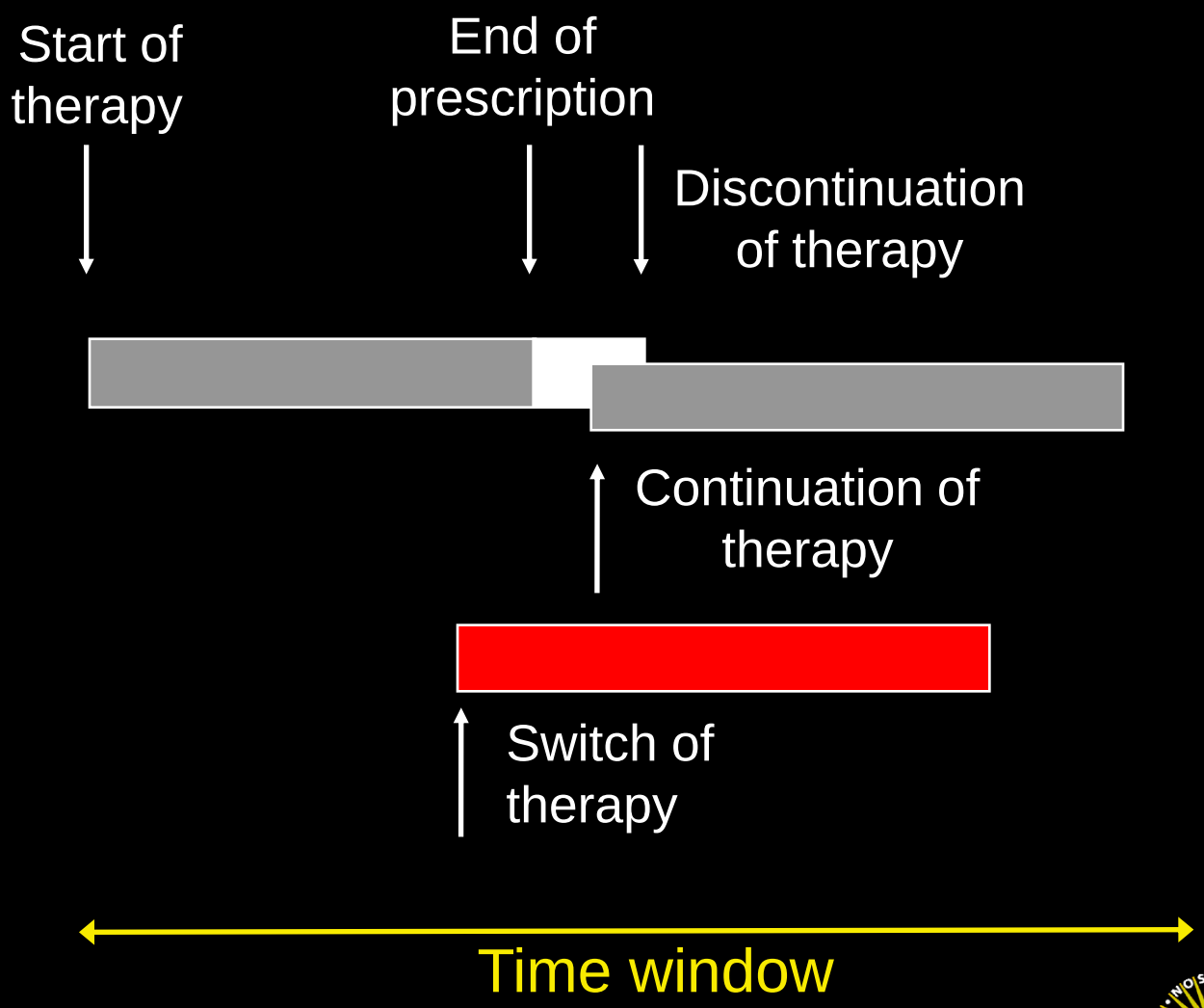
Design and Setting Follow-up of a group of biologicals approved in the United States and/or European Union between January 1995 and June 2007. Vaccines, allergenic products, and products for further manufacture and transfusion purposes were excluded.

Main Outcome Measures Nature, frequency, and timing of safety-related regulatory actions defined as (1) dear healthcare professional letters (United States) and direct healthcare professional communications (European Union), (2) black box warnings (United States), and (3) safety-related marketing withdrawals (United States and European Union) issued between January 1995 and June 2008.

BIOLOGICALS, DEFINED AS PRODucts of which the active substance is produced by or extracted from a biological source, represent an important and growing part of the therapeutic arsenal.[1] In the United States, the first bio-

JAMA 2008; 300: 1887-1896.

Drug exposure patterns and time windows



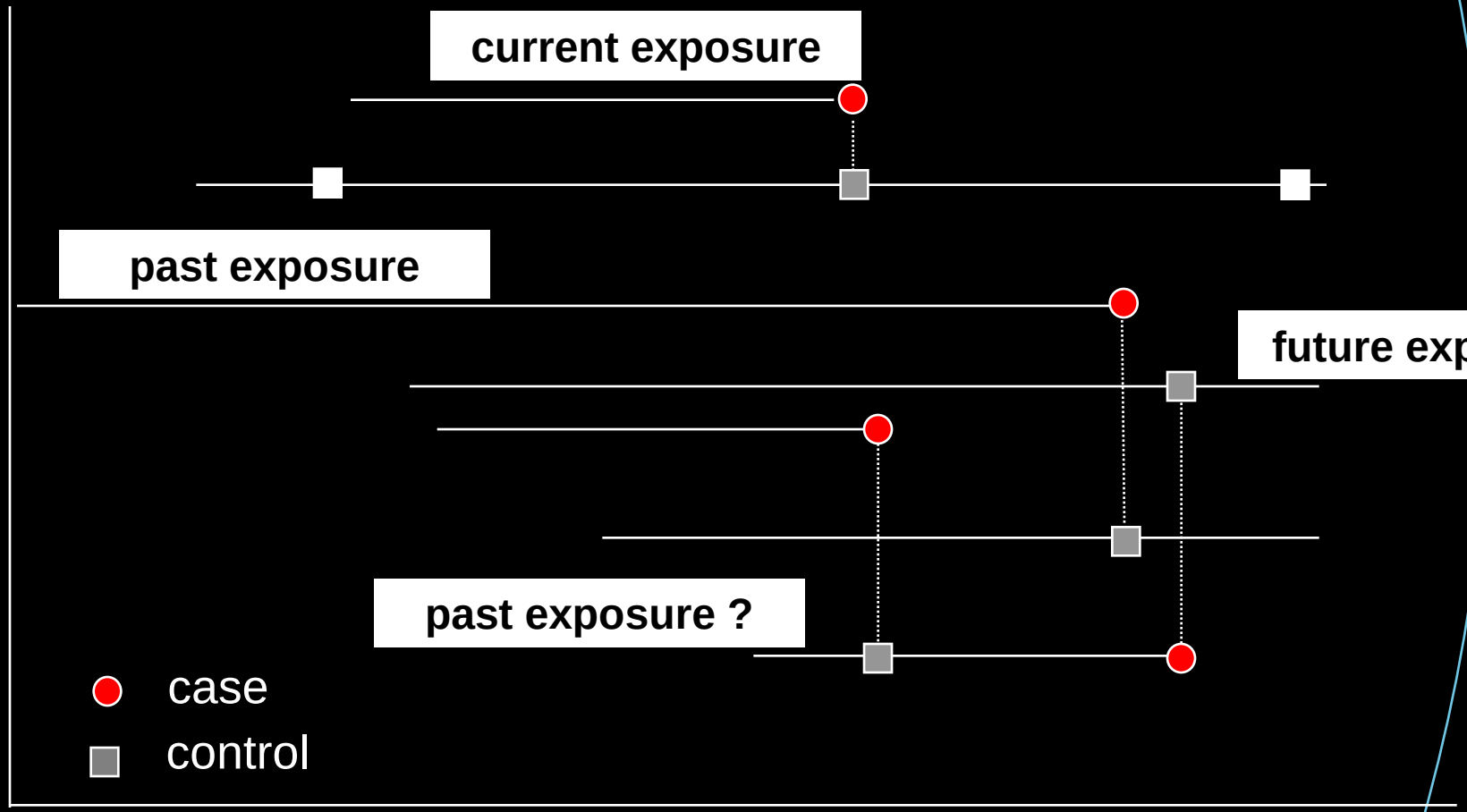
The effect of choice of time window on outcome*

Time window	Rate (CI 95%) (per 10^3 person-days)
Legend duration	0.7 (0.5-0.8)
7 day	0.6 (0.3-0.9)
30 day	0.6 (0.5-0.7)
60 day	0.5 (0.4-0.6)
90 day	0.4 (0.3-0.5)

* start of anti-ulcer therapy as marker for GI complaints

Staa TP van, Abenhaim L, Leufkens H. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. J Clin Epidemiol 1994; 47:183-9.

Drug exposure scenarios in a case-control fashion



Long-term proton pump inhibitor therapy and risk of hip fracture

Table 2. Risk of Hip Fracture Associated With Increasing Cumulative Duration of Proton Pump Inhibitor Therapy

	Cumulative Proton Pump Inhibitor Therapy Duration, y			
	1	2	3	4
OR (95% CI)*				
Crude	1.43 (1.35-1.52)	1.84 (1.67-2.01)	2.10 (1.91-2.35)	2.17 (1.93-2.45)
Adjusted†	1.22 (1.15-1.30)	1.41 (1.28-1.56)	1.54 (1.37-1.73)	1.59 (1.39-1.80)

Abbreviations: CI, confidence interval; OR, odds ratio.

*The ORs are from the conditional logistic regression model matched by year of birth, sex, and both calendar period and duration of follow-up before the index date, and included a quadratic term for duration of proton pump inhibitor therapy in years ($P<.001$ for the test of significance for the quadratic term).

†Adjusted for matching variables and all potential confounders in Table 1.

Yang YX et al JAMA 2006; 296(24): 2947-53.

Long-term proton pump inhibitor therapy and risk of hip fracture (II)

Table 1. Characteristics of Hip Fracture Cases and Controls*

	Cases (n = 13 556)	Controls (n = 135 386)	Crude OR (95% CI)
Female sex	79.90	79.89	NA
Age at database enrollment, mean (SD), y	77 (9.3)	77 (9.3)	NA
Body mass index†			
<20	6.77	3.59	1.95 (1.82-2.10)
>30	4.51	6.71	0.65 (0.60-0.71)
Medication use			
Anxiolytic	14.95	9.20	1.76 (1.67-1.85)
Antidepressant	8.42	4.09	2.17 (2.03-2.32)
NSAID/aspirin	9.16	6.84	1.38 (1.30-1.47)
Thiazide diuretic	5.85	6.05	0.95 (0.89-1.04)
Antipsychotic	4.46	1.39	3.34 (3.03-3.67)
Antiparkinsonian	3.49	0.94	3.83 (3.44-4.26)
Antiseizure	2.26	0.68	3.42 (3.00-3.90)
Hormone therapy	0.74	1.03	0.53 (0.39-0.71)
Corticosteroid	3.15	1.43	2.25 (2.02-2.51)
Thyroxine	5.09	3.69	1.40 (1.29-1.52)

Yang YX et al JAMA 2006; 296(24): 2947-53.

Use of beta2 agonists and risk of MI in patients with hypertension

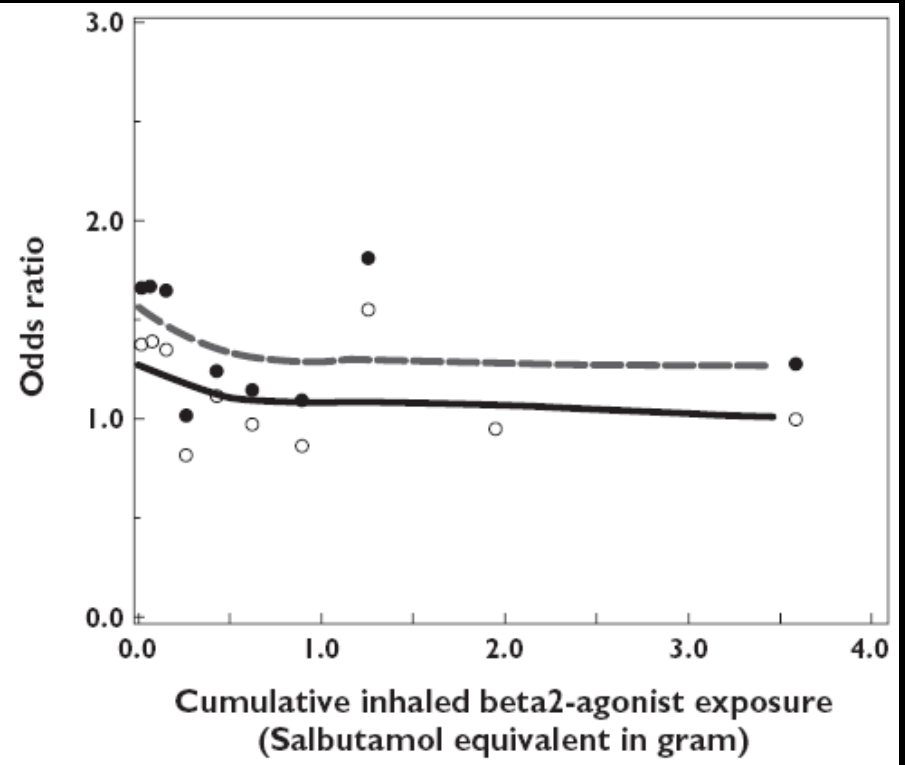
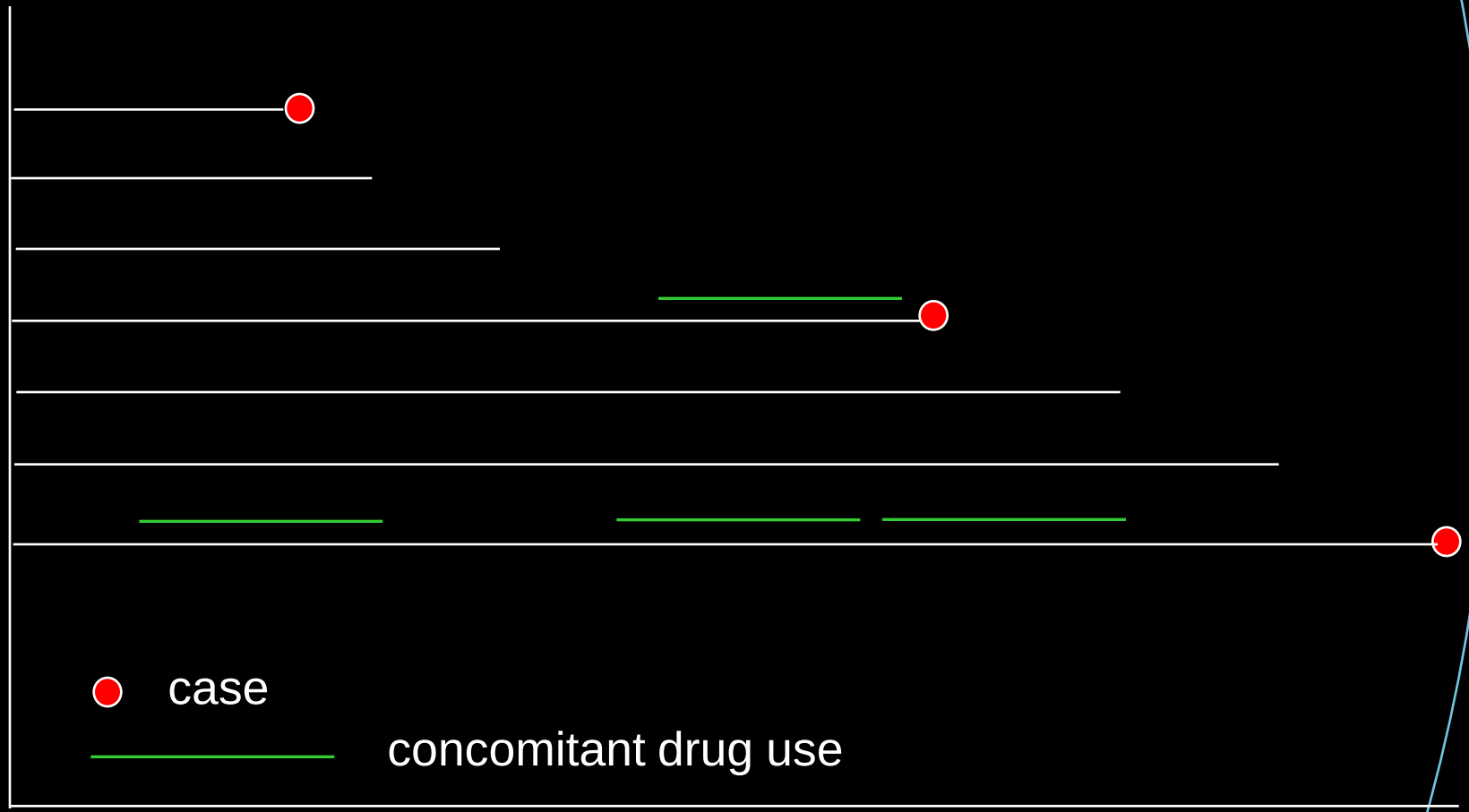


Figure 2

Risk of acute myocardial infarction (MI) and cumulative dose of β_2 agonists use among current users. Adjusted for confounders in Table 2 (model under footnote †). Adjusted odds ratio (——); Crude odds ratio (– – –)

Vries F de, et al. Br J Clin Pharmacol 2008; 65: 580-6.

Drug exposure scenarios in a cohort fashion



Duration of antihypertensive drug use and risk of dementia

Table 3 Hazard ratios (HR) of all dementia and Alzheimer disease with use of antihypertensive drugs

	All dementia (n = 527)			Alzheimer disease (n = 432)		
		HR (95% CI)			HR (95% CI)	
	Cases	Model I*	Model II†	Cases	Model I*	Model II†
Never use	263	1.00 (ref)		214	1.00 (ref)	
Antihypertensive drug use						
<1.6 y	126	0.94 (0.75–1.17)	0.90 (0.72–1.13)	102	0.92 (0.73–1.18)	0.91 (0.71–1.17)
1.6–5.3 y	98	0.77 (0.60–0.99)	0.72 (0.56–0.93)	83	0.75 (0.57–0.98)	0.73 (0.55–0.96)
>5.3 y	40	0.71 (0.49–1.03)	0.68 (0.47–0.99)	33	0.70 (0.47–1.05)	0.69 (0.46–1.05)
Per year treatment	264	0.95 (0.91–1.00)‡	0.95 (0.90–0.99)	218	0.95 (0.90–0.99)	0.94 (0.90–0.99)

*Model I: age, sex, and systolic and diastolic blood pressure adjusted.
†Model II: as model I, additionally adjusted education, smoking, total serum cholesterol, body mass index, diabetes mellitus, and cardiovascular and cerebrovascular disease.
‡Upper limit of confidence interval <1.00, $p < 0.05$.

Haag MD et al. Neurology. 2009 Feb 18.

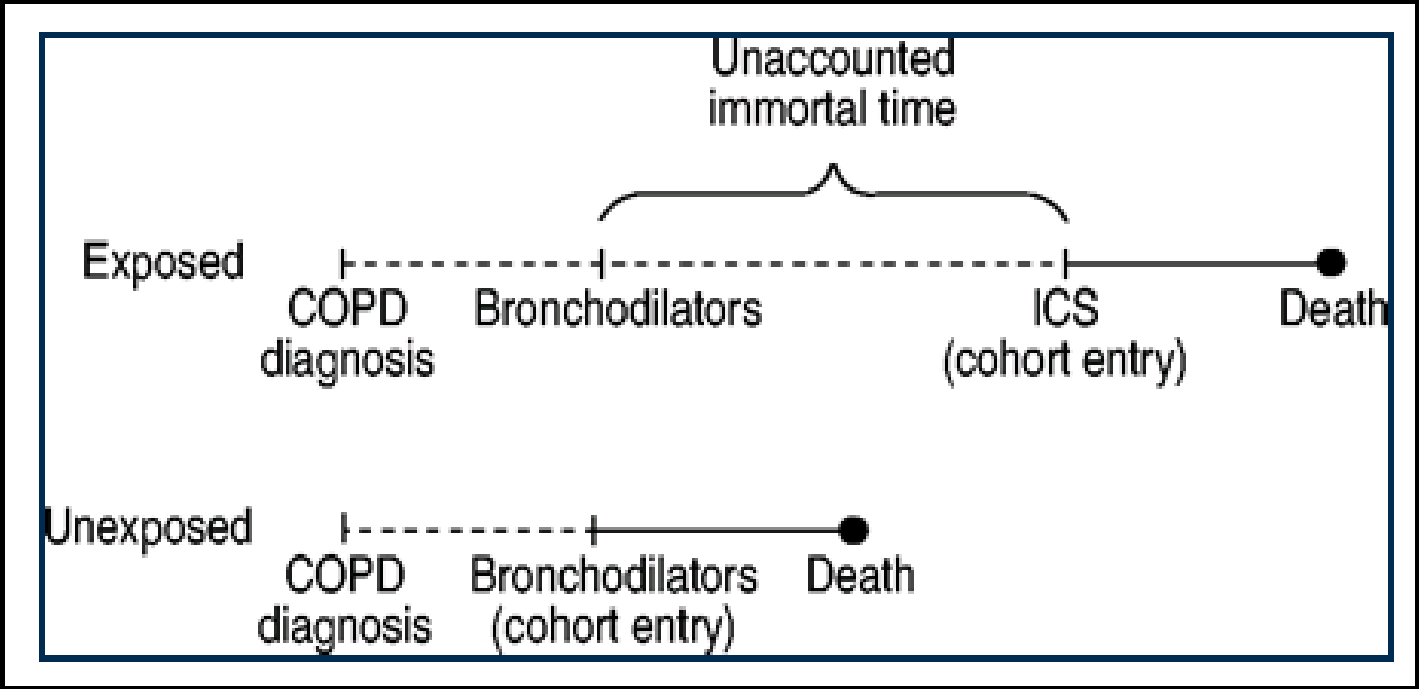
Duration of antihypertensive drug use and risk of dementia (II)

Assessment of drug exposure. Complete data on filled prescriptions were available on a day-to-day basis from the pharmacy prescription database in automated form. This included the product name, international non-proprietary name, Anatomic Therapeutic Chemical (ATC) code, total number of delivered units (e.g., tablets/capsules), prescribed daily number of units, date of delivery, and drug dosage. The duration of a prescription is calculated as the number of delivered units divided by the prescribed daily number of units.

In addition to overall antihypertensive use, we distinguished among the most commonly used types of antihypertensive drugs in the Netherlands, as classified by ATC code. These included β-blocking agents, thiazides and high ceiling diuretics, calcium-channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin-2 (AT2) antagonists, and other antihypertensive drugs (centrally acting sympathicolytics, peripheral acting sympathicolytics, and agents acting on arteriolar smooth muscle).

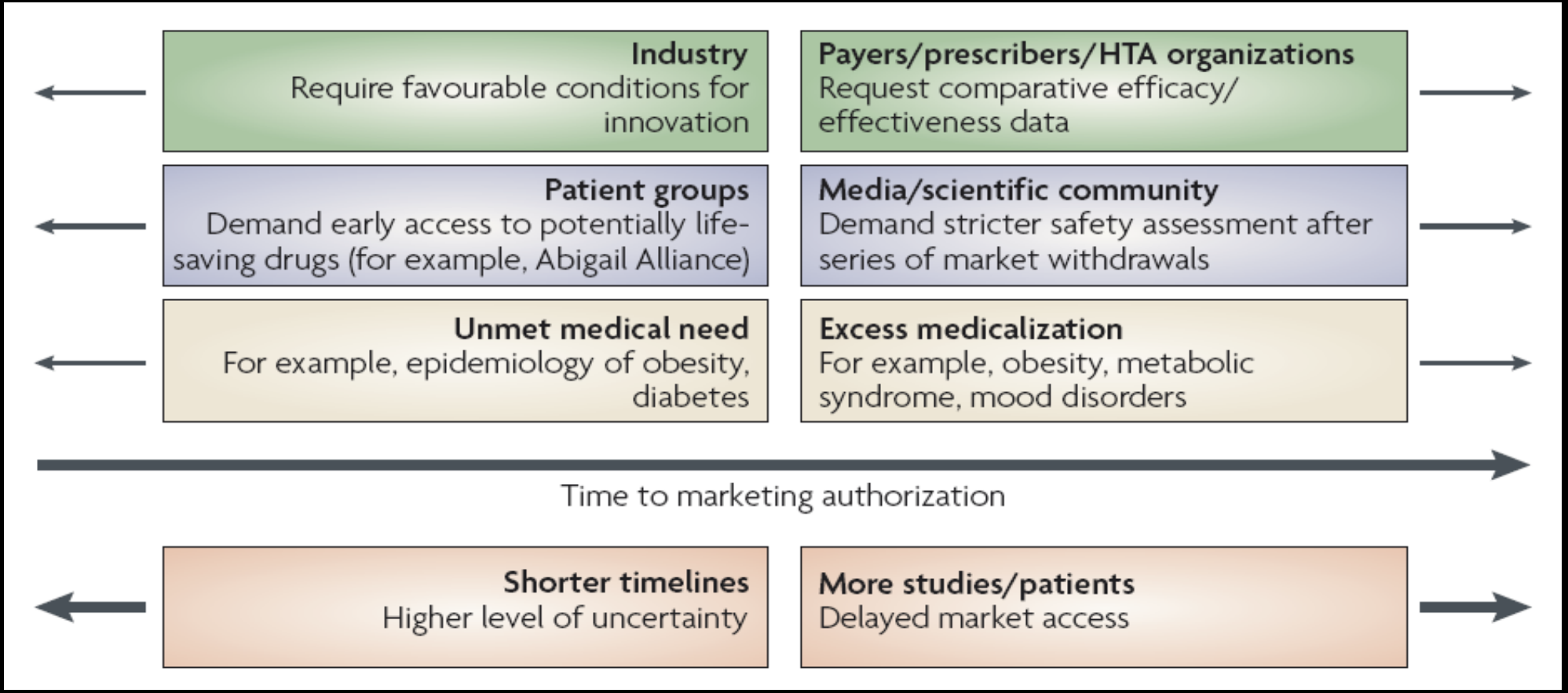
Haag MD et al. Neurology. 2009 Feb 18.

Immortal time bias in cohort studies



Suissa S. Am J Repir Crit Care Med 2003; 168; 49-53

Regulatory science agenda



Eichler H-G, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data: a mounting dilemma. Nature Drug Disc 2008; 7(10): 818-26.

Anchors for needs and opportunities for database collaboration

- Regulators, prescribers and other decision makers are in need of the strongest evidence available for B/R assessment.
- Drug exposure ascertainment, both qualitative and quantitative, is key to every B/R assessment.
- There is no single approach, centre or database that can solve all the issues.
- Multi-data base collaboration (e.g. NorPEN, ENCePP, etc) deserves full commitment and the willingness to learn and share.