

50 years of pharmacovigilance: unfinished job

Joan-Ramon Laporte

The role of pharmacoepidemiology in medicines regulation

15th ENCePP Plenary Meeting

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European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance



EUROPEAN MEDICINES AGENCY
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108 market withdrawals in F, D & UK, 1961-93

Liver toxicity

24

Blood dyscrasias

12

Neuropsychiatric

11

Cutaneous

9

Fulminant hepatitis

Agranulocytosis

Aplastic anaemia

Thrombocytopenia

Guillain-Barré syndrome

Stevens-Johnson syndrome

Toxic epidermal necrolysis



First-generation pharmacovigilance

Attention to «unexpected» ADRs, of low incidence.

Series of cases.

Spontaneous reporting.

Series of cases at hospital emergency departments.

Clinical perspective: latency, clinical manifestations, outcome.

- It does not inform on incidence.
- It does not inform on risk.



108 market withdrawals in F, D & UK, 1961-93

Incidence
(n per 10⁶ and year)

Liver toxicity

24

Fulminant hepatitis

5-10

Blood dyscrasias

12

Agranulocytosis

3-5

Aplastic anaemia

2

Neuropsychiatric

11

Thrombocytopenia

15-20

Cutaneous

9

Guillain-Barré syndrome

15-20

Stevens-Johnson syndrome

1

Toxic epidermal necrolysis

<1



Incidence
(n per 10⁶ and year)

Breast cancer	300
Gastrointestinal haemorrhage	400
Death by MI	870
CVA	2,300
Hospital admission by IC	2,200
Fall and hip fracture	800-1,400
Death by cancer (all)	1,730



NSAIDs
Antiplatelet drugs
Anticoagulants

NSAIDs
Diuretics
ACEI, ARB

Statins

Gastrointestinal haemorrhage

Type 2 diabetes

Acute renal failure

NSAIDs
Hormonal contraceptives
Glitazones

CV mortality and morbidity

Fall and hip fracture

PPIs
Psychotropic drugs
Opiate analgesics
Antihypertensive drugs

Dementia, Alzheimer disease

Sudden death

Hypnotics
Anticholinergic drugs

H₁ antihistamines
Antipsychotic drugs



Number needed to treat, NNT

$$AR = RE - R\bar{E}$$

$$NNT = \frac{1}{AR} \times 100$$

NNH: Number Needed to Harm



The risk can be estimated.

The relative risk gives a clinical and epidemiological perspective.

The attributable risk depends on the incidence and the relative risk.

It informs on the public health impact of the ADR.



Second-generation pharmacovigilance

Observational studies.

Electronic databases.

Predominantly common conditions.

Informs on the relative risk, but not always on incidence.

- Biases inherent to observational research.
- Promotion and publication bias.
- Useful to support decision taking?



Electronic Health Data for Postmarket Surveillance: A Vision Not Realized

Thomas J. Moore^{1,2} · Curt D. Furberg³

ed. When just one mid-sized clinical trial can cost tens of millions of dollars, the idea that clinical safety data of similar quality can be obtained from millions of electronic health records at minimal cost is naïve at best. Because it is



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Key Points

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Electronic health data for postmarket surveillance became a key element in the new paradigm for drug regulation, which involved fewer and smaller clinical trials prior to marketing approval.

The research programs and pilot systems created to study harms of licensed drugs proved largely unable to provide credible evidence of new, unsuspected drug adverse effects, and conflicting and contradictory results when seeking to confirm known harms.



Finally, it is important for regulators and the medical community to understand that a critical element of the new paradigm—rapid and intensive drug surveillance through electronic health data—is nowhere near at hand.

It does not now provide a viable safety net to counterbalance ‘innovation promoting’ drug approval policies that are reducing the number, size, rigor, and duration of randomized clinical trials.



Meta-analysis of RCTs

- HRT – Breast cancer, PTE, CVA, MI, dementia.
- Rofecoxib, other NSAIDs – MI and other cardiovascular.
- Antipsychotic medicines, dementia and mortality.
- SSRIs – Suicide (particularly children), violence.
- Epoetins – Hypertension, mortality.
- Inhaled anticholinergic drugs – MI and CV mortality.
- Antiepileptic drugs – Suicide.
- Ezetimibe + simvastatin – Cancer mortality.
- Rosiglitazone – MI.



Third-generation pharmacovigilance

RCTs and meta-analysis of RCTs.

Type A effects; relatively frequent.

Informs on relative risk and on incidence.

No observational biases: random distribution.

- Patients not representative of those in usual clinical practice.
- Difficult access to original patient data.
- Promotion and publication biases.



Open

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 96 NUMBER 2 | AUGUST 2014

Toward Enhanced Pharmacovigilance Using Patient-Generated Data on the Internet

RW White¹, R Harpaz², NH Shah², W DuMouchel^{3,4} and E Horvitz¹

The promise of augmenting pharmacovigilance with patient-generated data drawn from the Internet was called out by a scientific committee charged with conducting a review of the current and planned pharmacovigilance practices of the US Food and Drug Administration (FDA). To this end, we present a study on harnessing behavioral data drawn from Internet search logs to detect adverse drug reactions (ADRs). By analyzing search queries collected from 80 million consenting users and by using a widely recognized benchmark of ADRs, we found that the performance of ADR detection via search logs is comparable and complementary to detection based on the FDA's adverse event reporting system (AERS). We show...



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Fourth-generation pharmacovigilance

Patient-generated data drawn from the internet.
Harnessing behavioural data drawn from Internet search logs to confirm (and detect?) ADRs.



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ANALYSIS

Medical error—the third leading cause of death in the US

Medical error is not included on death certificates or in rankings of cause of death. **Martin Makary** and **Michael Daniel** assess its contribution to mortality and call for better reporting

Martin A Makary *professor*, Michael Daniel *research fellow*

Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

The annual list of the most common causes of death in the United States, compiled by the Centers for Disease Control and Prevention (CDC), informs public awareness and national

How big is the problem?

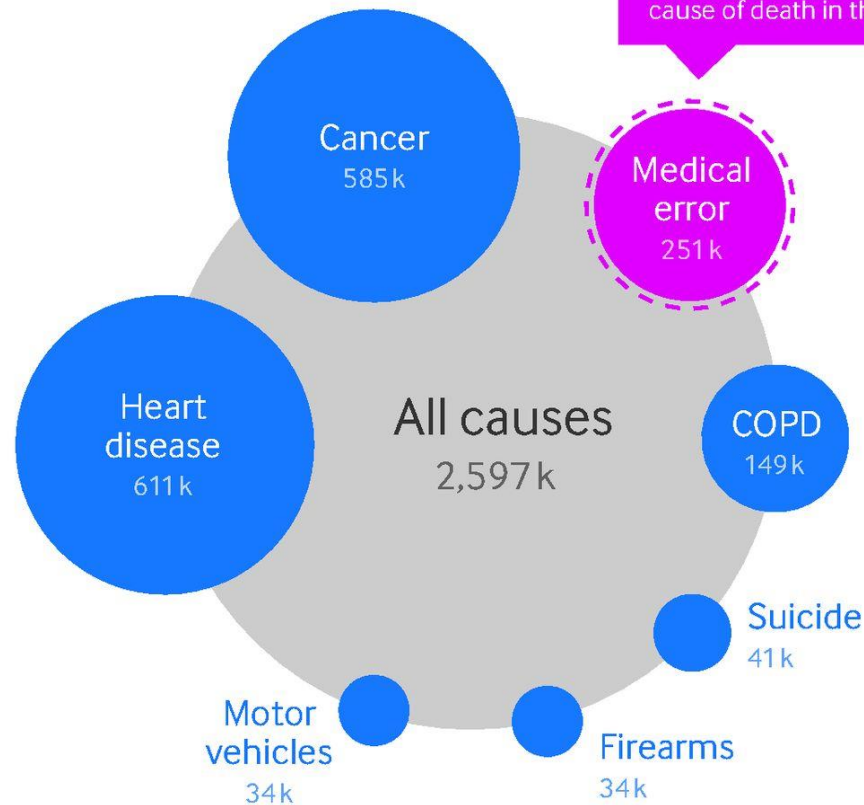
The most commonly cited estimate of annual deaths from



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Causes of death, US, 2013



Based on our estimate, medical error is the 3rd most common cause of death in the US

However, we're not even counting this - medical error is not recorded on US death certificates

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Data source:

http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf



Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies

Jacoline C. Bouvy^{1,2} · Marie L. De Bruin¹ · Marc A. Koopmanschap²

Review of studies “quantifying” ADRs in a European setting

- Emergency rooms (22 studies).
- Patients admitted to hospital (13 studies).
- Outpatient settings (5 studies).



Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies

Jacoline C. Bouvy^{1,2} · Marie L. De Bruin¹ · Marc A. Koopmanschap²

- 3.6% of hospital admissions (22 studies).
- 12.3% of hospital admissions in the elderly (3 studies).
- 10.1% of hospitalized patients (13 studies).



L. Juntti-Patinen · P.J. Neuvonen

Drug-related deaths in a university central hospital

- Detailed chart review.
- One-year period (1,511 deaths).
- 5% of all deaths were caused by an ADR.
- 0.05% of all hospitalizations resulted in a fatal ADR.
- In line with the results of other studies.



Epidemiology of Adverse Drug Reactions in Europe:

- A
- Jac
- 83.6×10^6 patients are hospitalized each year (31 countries, 504×10^6 inhabitants).
 - 0.5% of fatal in-hospital ADRs would give 419,000 deaths per year.
 - 0.05% would give 42,000 deaths per year.



Burden of drug-induced disease

- If ADRs are one of the main causes of disease, disability, and death, what are the specific causes?



Burden of drug-induced disease

- Haemorrhage induced by oral anticoagulants.
- Haemorrhage induced by low molecular weight heparins.
- Upper gastrointestinal bleeding associated with NSAIDs.
- Upper gastrointestinal bleeding associated with antiplatelet drugs.
- Anaemia in users of NSAIDs or antiplatelet drugs.
- Hip fracture in the elderly associated with psychotropic drugs, antihypertensive drugs, and other medications.
- Ischemic heart disease associated with NSAIDs.
- Decompensated CHF associated with NSAIDs.



Burden of drug-induced disease

- Severe asthma, near death and death with β -adrenergic blocking agents.
- Drug-induced hyperkalemia (particularly in relation to ACEIs, spironolactone, and β -adrenergic blocking agents).
- Drug-induced hyponatremia, with emphasis on hyponatremia induced by SSRI antidepressants.
- Diabetes, obesity, and metabolic syndrome with atypical and typical antipsychotic drugs.
- Acute renal failure associated with ACEI, loop diuretics, statins, NSAIDs, several antibiotics, contrast media, and other drugs.



Burden of drug-induced disease

- Traffic accidents and CNS depressant medications.
- Parkinsonism and antipsychotic and other drugs (e.g., metoclopramide).
- Severe infection by immunosuppressants in rheumatology.
- Cancer by immunosuppressants (topical and systemic).
- Breast cancer and hormone replacement treatment (HRT).
- Pseudomembranous colitis induced by broad-spectrum antibiotics.

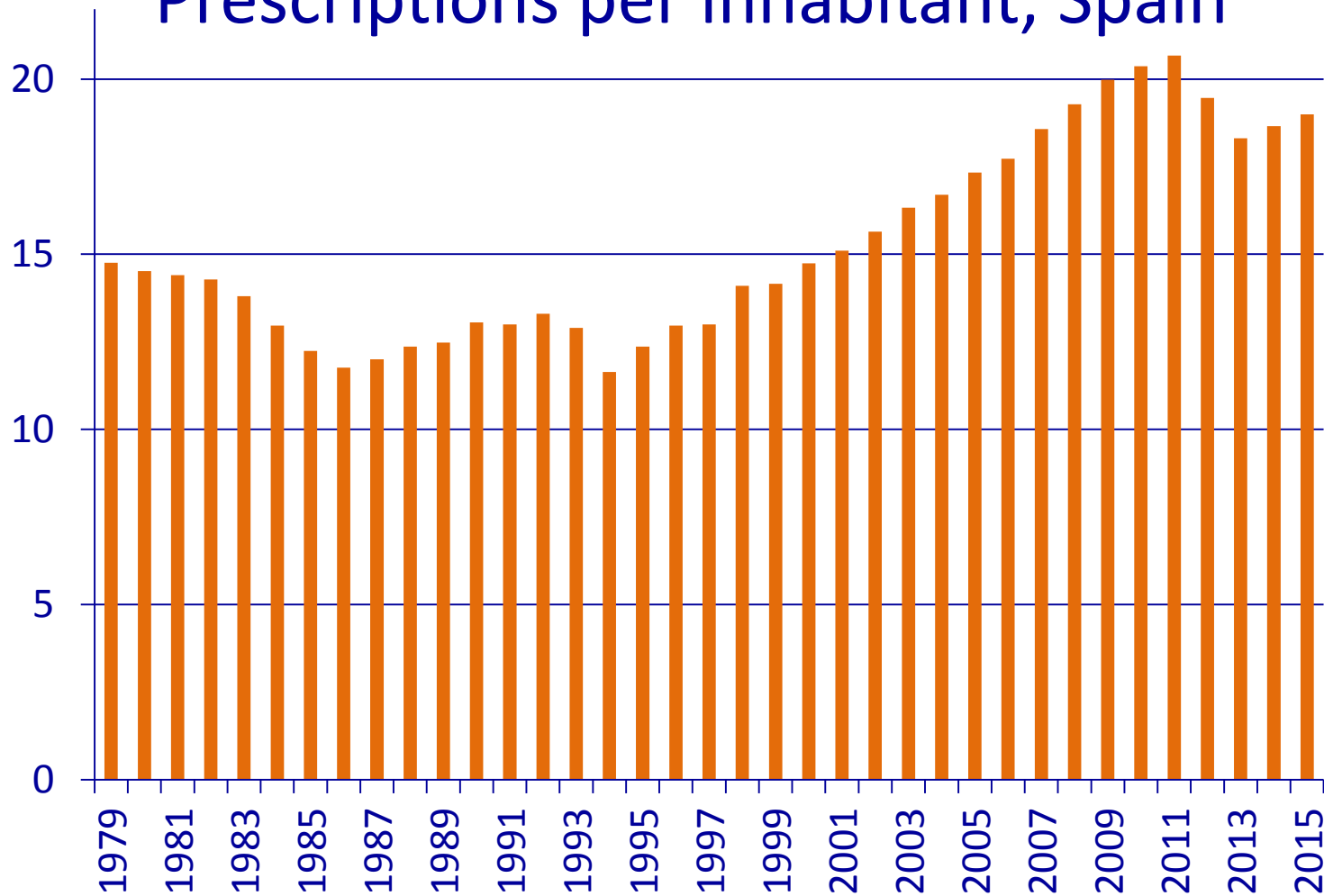


- If ADRs are one of the main causes of disease, disability, and death, what are the specific causes?

- Pay attention to utilization patterns.



Prescriptions per inhabitant, Spain

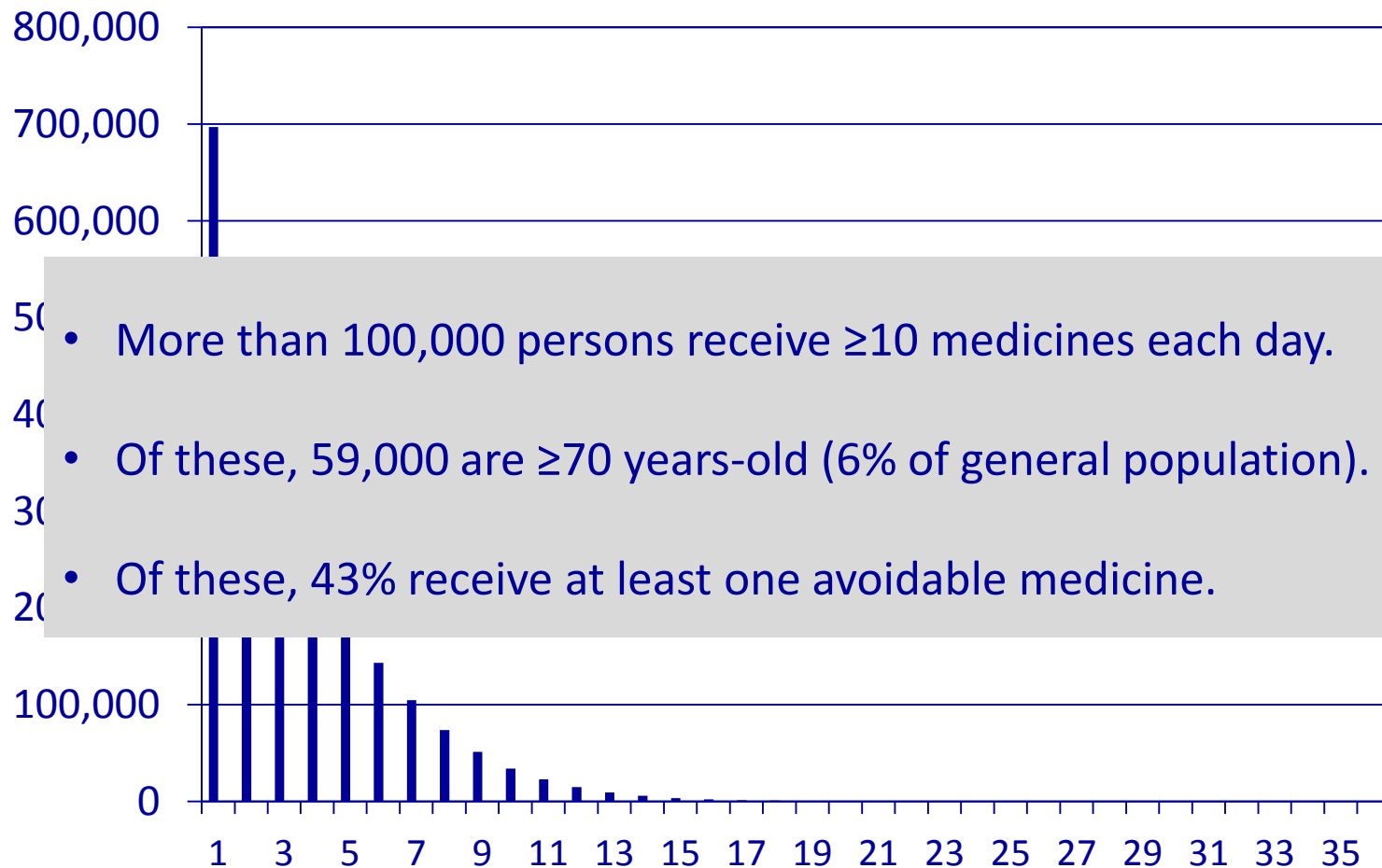


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Increase in the consumption of medicines

- Higher number of exposed people.
- During longer periods (long-term effectiveness and harms).
- With a higher number of medicines (interactions).

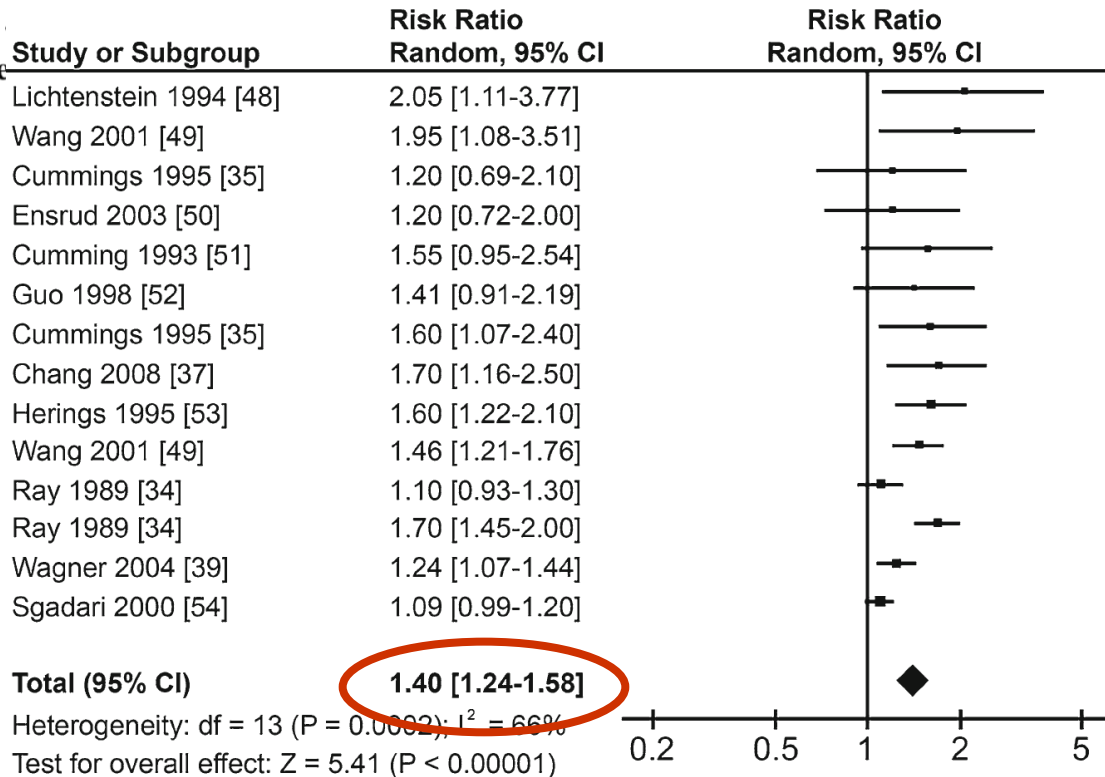




ORIGINAL RESEARCH

Potential Impact of Benzodiazepine Use on the Rate of Hip Fractures in Five Large European Countries and the United States

T. P. Khong
 O. H. Klunge
 H. Petri



Consumption of hypnotics & sedatives, DDD per 1,000 inhabit and day, 2009

Country	DDD	SAB	LAB
France	76.0	64.1	11.9
Germany	18.0	14.0	3.91
Italy	52.4	42.4	10.0
Spain	85.5	67.9	17.6
UK	19.3	11.6	7.63
US	82.9	75.9	6.96

DDD WHO's defined daily dose, *SAB* short-acting benzodiazepine, *LAB* long-acting benzodiazepine



Attributable risk (% of all hip fractures) 2009

France	7.4 (4.5–10.3)
Germany	1.8 (1.2–2.4)
Italy	2.0 (1.2–2.8)
Spain	8.0 (4.9–11)

Every year, in Catalonia, 746 hip fractures attributable to hypnotics & sedatives



Antidepressants

Osteoporos
DOI 10.100

Table 1 Differences in antidepressant use (in DDDs/1,000 persons/day) in the five large EU countries and the USA calculated by using IMS drug sales data (2009)

ORIGIN	Country	Total	SSRIs	TCAs
Exces of ant D. Prieto- T. P. Kho	France	49.94	31.99	3.47
	Germany	39.68	18.30	10.20
	Italy	38.05	28.71	1.72
	Spain	62.48	42.70	2.96
	UK	64.95	44.51	9.57
	USA	97.50	66.29	5.04

DDD_s/1,000/day shown are not corrected for the ratio (mean DDD_s/1,000 persons/day) : (DDD_s/1,000 persons/day)



Hip fracture and medicines

Pharmacological group	N of cases per year
PPIs	>1,300
Hypnotics & sedatives	746
Antidepressants	650
Neuroleptic drugs	150-300
Opiate analgesics	?
Antihypertensive drugs	?

Add the use of combinations!



Adverse effects and public health in Catalonia

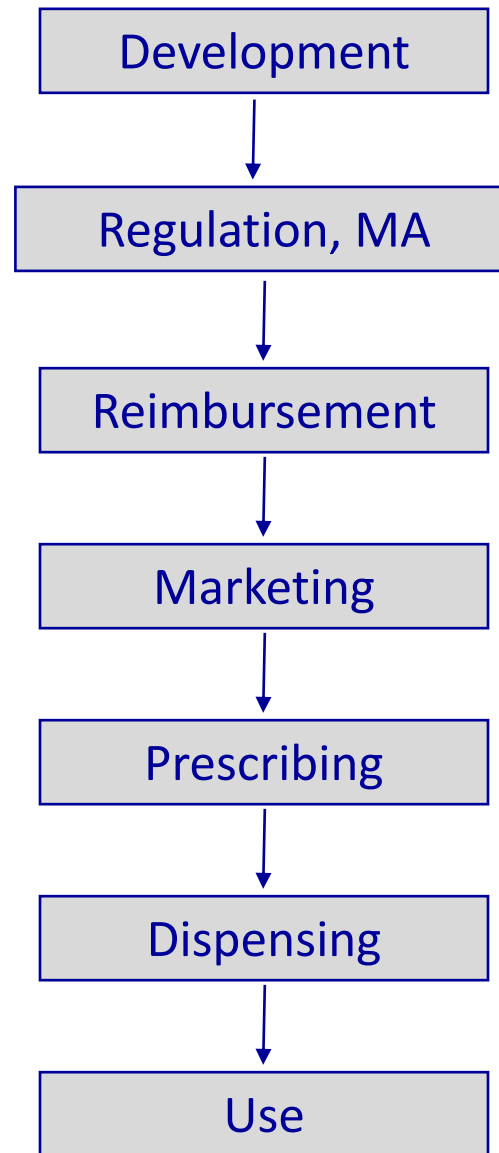
- More than 10,000 cases of severe haemorrhage attributable to OAC & AP.
- 1,400 admissions for GI haemorrhage – other drugs, 150 deaths.
- 100-300 cases of sudden death – neuroleptic drugs.
- 1,800-2,400 cases of diabetes – statins.
- An undetermined number of cases of dementia and AD – hypnotics, sedatives, and other.
- Substantial cardiovascular mortality – epoetins.



Adverse effects and public health in Catalonia

- Hundreds of hospital admissions for HF – NSAIDs, epoetins, other).
- Around 100 cases of MI, arrhythmia and CVA – diclofenac and other NSAIDs.
- Around 600 cases of atrial fibrillation – bisphosphonates.
- 50-150 cases of hospital admission for pneumonia– PPIs, hypnotics & sedatives.





Objectives in pharmacovigilance

- Detecting unknown adverse effects.
 - Risk evaluation (incidence, prevalence).
 - Risk minimization (risk groups).
 - Risk communication.
-
- Patient's safety and public health perspective.



I

(Legislative acts)

REGULATIONS

**REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 15 December 2010**

amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products

(Text with EEA relevance)



DIRECTIVES

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2010

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

- (3) In the light of the experience acquired and following an assessment by the Commission of the Union system of pharmacovigilance, it has become clear that it is necessary to take measures in order to improve the operation of Union law on the pharmacovigilance of



- A broadening of the definition of ADR (medication errors, off-label use, misuse, abuse).
- Eudravigilance database as the single SR database.
- Reporting by patients.
- Company-driven RMPs.
- No obligations for EMA to perform or to promote independent observational research and cumulative meta-analyses of RCTs, or to collaborate with other institutions in the development of new methods.



- No reference to Regional Centres of Pharmacovigilance.
- No reference to the role of healthcare organizations.
- No reference to the need for monitoring national and local DU patterns.
- No specific provisions for intensive monitoring of innovative biotechnological products and other innovative products.
- Based on spontaneous reporting and company-driven RMPs.



Big data

Active surveillance

Regulatory science

Real-world evidence

Adaptive pathways



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Conclusions



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Medicines, even if reasonably safe, can cause substantial burden of disease

The use of medicines is an important cause of disease, disability, and death.

(But we can say little more than this)

Much of this harm is caused by drugs with an acceptable B/R ratio (PPIs, statins).

An undetermined proportion is caused by treatments which are avoidable, unnecessary, or too long.



For a healthy use of medicines

A substantial proportion could have been **prevented**:

- By avoiding the MA or reimbursement of new medicines which do not represent a **therapeutic advantage** (efficacy, unsafety, convenience, or cost).
- By promoting a **healthy medicines prescribing**, individualized for each patient.
- By preventing the undue influence of drug companies on prescribing determinants.
- With a more robust structure of pharmacovigilance.



Ineffective regulation?

A large extent of the data of interest on beneficial and adverse effects of drugs are made public at least 10 years after launch, when the drugs are already in wide usage.

EU legislation on pharmacovigilance relies on centralized evaluation of SR and RMPs. This is inadequate.

But regulation is only one step in the medicines chain.



Vigilance of medicines unsafety or vigilance of patients' unsafety?

- Proactive and preventive pharmacovigilance.
- Linked to communication with prescribers.
- With special attention to innovative treatments.



Innovation is a priority

Registry of treated patients, CatSalut:

- 139,733 registered treatments.
- 96,968 patients.
- 303 indications.
- 152 different drugs.
- Eight therapeutic areas (Oncology, HIV, MS, HCV, etc.).
- 64 hospitals.



Understand the influence of the various steps of the medicines chain.

Unsafety in the context of an, often unnecessary, polymedication.

ADRs occur in the society and in the health system.

Patient's safety, a priority of healthcare provider organizations.



Regional centres of PhV and patients' safety

- To promote, assemble and evaluate spontaneous reports.
- Embedded within the local health care system.
- Patients' safety should be a priority of Drug & Therapeutic Committees.
- Establish robust relationships with prescribers, as support, rather than as a control.



Regional centres of PhV and patients' safety

- To monitor the patterns of use of new and old medicines and treatments, in order to identify the areas with a greater public health impact:
 - Medicines without proof of efficacy.
 - Unnecessary treatments.
 - Unnecessarily long treatments.
 - Other forms of dangerous use (contraindications, risk of adverse interactions).



Regional centres of PhV and patients' safety

- Research on the main causes of mortality, disability and disease induced by medicines.
- Continuous medical education, information on medicines and therapeutics.
- Health education – media.

Avoid conflicts of interest



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