

# Basic Principles of Pharmacovigilance and Data Sources

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# Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

*WHO*

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# Pharmacovigilance

- ✓ collects, records, codes ADEs / ADRs
- ✓ analyses and assesses the reports
- ✓ promotes the safe use of drugs
- ✓ creates appropriate structures and means of communication needed to perform its tasks

# Aims of Pharmacovigilance

- ✓ to improve patient care and safety
- ✓ to improve public health and safety
- ✓ to contribute to the assessment of benefit, harm, effectiveness and risk of medicines
- ✓ to promote education and clinical training
- ✓ to promote effective communication to the public
- ✓ to promote rational and safe use of medicines

# Reaction / Adverse Drug Reaction

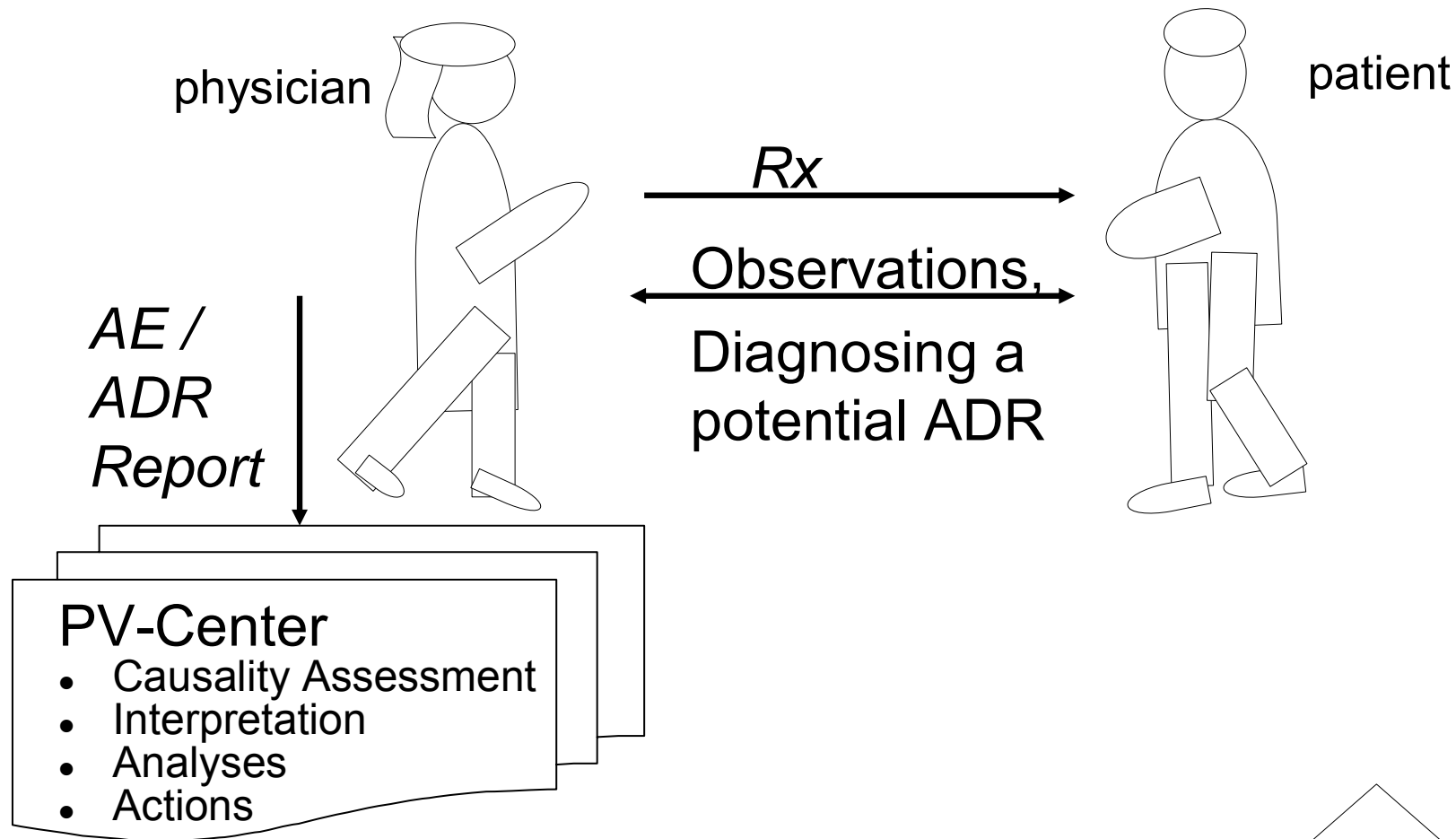
Adverse Reaction means a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

*A reaction, contrary to an event is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or a reviewing health care professional.*

# Pharmacovigilance - Data Sources

- ✓ Spontaneous Reporting Systems
  - National PV Centre / Drug Authority
  - from the published scientific literature and Drug Bulletins
- ✓ Adverse Reaction Case Reports by the MA holder (e.g. collected by sales representatives)
- ✓ Periodic Safety Update Report (PSUR) provided by MA holder

# Basic Model of Pharmacovigilance



# Limitations of Spontaneous Reporting

- Underreporting      ➔ Nominator ?  
Incidence ?
- Number of exposed people      ➔ Denominator ?  
Incidence ?
- Quality and missing data      ➔ Valid Assessment ?  
Causality ?
- Causality Assessment      ➔ Limited reliability



# Leading Role of Spontaneous Reporting

- ✓ covers all drug use of all populations
- ✓ 13/18 of the most important ADRs before 1982 have been 'signaled' for the first time by SRs (*Venning 1983*)
- ✓ More than 50% of all 'alert' black boxes in the PDR derive from SRs (*Beach 1998*)

# How to improve Spontaneous Reporting Systems?

- ✓ Regionalisation
- ✓ Combination with DIC-activities
- ✓ Retrieval of additional information
- ✓ Access to all relevant pre- and post-marketing information
- ✓ Access to detailed drug utilization data
- ✓ Standardized Assessment of causality and seriousness
- ✓ Stimulation

# Assessment of AE / ADR-Reports

- ✓ Seriousness / Severity
  - ICH
  - NCI
- ✓ Frequency
- ✓ Causality
- ✓ Pattern, e.g. pre-disposing risk factors

# Adverse Reaction Report - minimum information

- ❑ an identifiable source
- ❑ a patient
- ❑ a suspected product
- ❑ a suspected reaction

# **Serious Adverse Reaction**

**Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation, or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly / birth defect.**

## GASTROINTESTINAL

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		Grade				
Adverse Event	Short Name	1	2	3	4	5
<p><b>NAVIGATION NOTE:</b> Abdominal pain or cramping is graded as Pain – Select in the PAIN CATEGORY.</p>						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
<p>ALSO CONSIDER: Weight loss.</p>						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
<p><b>REMARK:</b> Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chyloous ascites.</p>						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
<p>ALSO CONSIDER: Hemorrhage, GI – Select.</p>						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; constipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
<p>ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – Select.</p>						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
<p>ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.</p>						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

# Causality Assessment

## PROBLEM

There is a large interobserver variability when assessing the causality of a single ADE-report.

Decision algorithm may help to assess reliably causality and to identify causes for disagreement.

# Causality Assessment

## MAJOR CRITERIA

- Has the suspected drug actually been administered?
- Is the time interval between drug administration and occurrence of the ADR adequate?
- Is there an alternative reasonable cause for the AE?
- Did the AE disappear once the suspected drug was withdrawn or reduced (Dechallenge)?
- Did the AE reoccur once the suspected drug was re-administered (Rechallenge)?
- Where the drug levels measured and in favor of a type A reaction?
- Had the patients a disposition for this ADR?



# Terms for Description of Causality

 unrelated

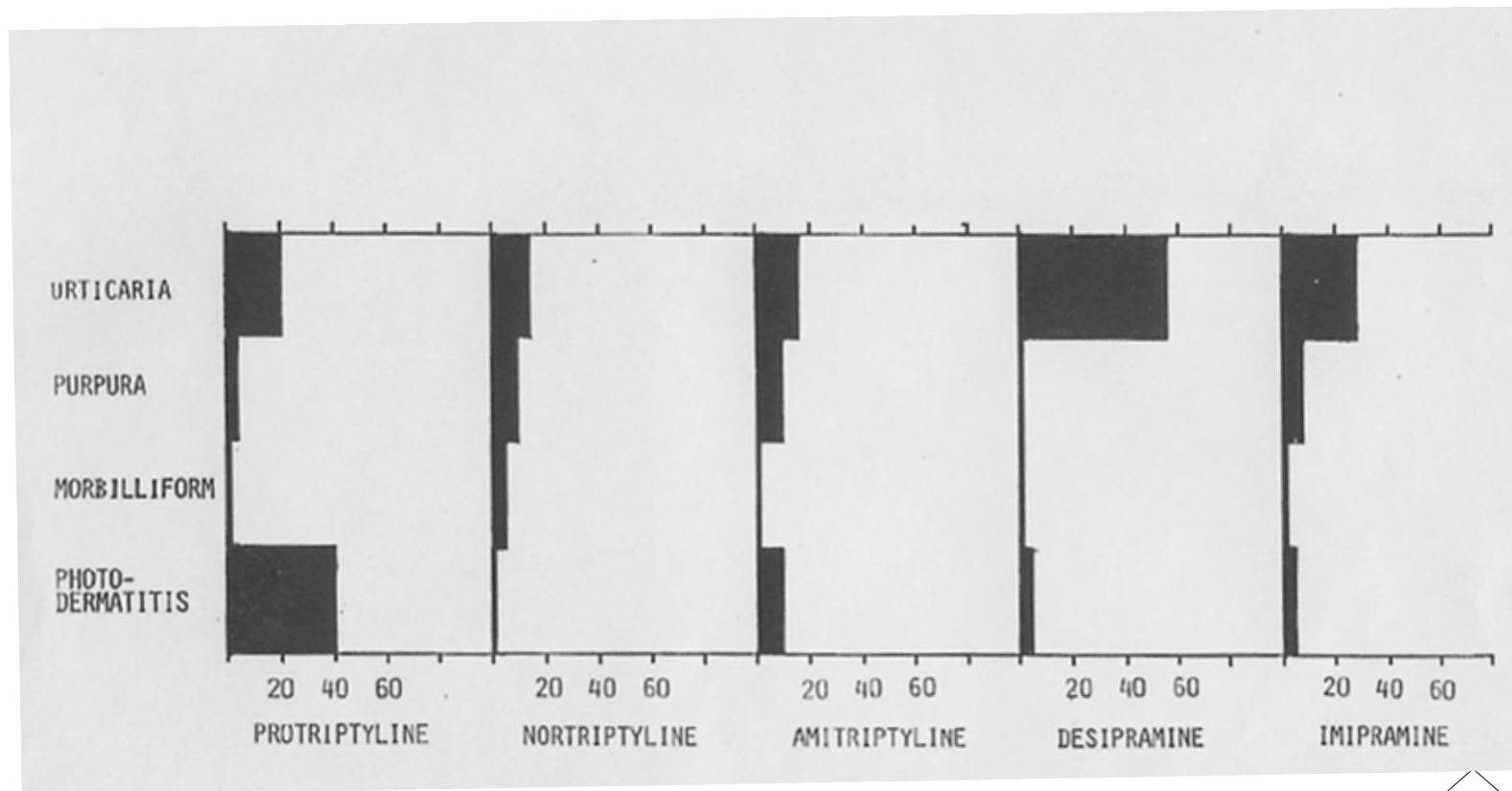
 possible

 probable

 definite

 not assessable

# Profile of cutaneous reactions of tricyclic Antidepressants



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# Signal - Definition

A signal is a set of data constituting a hypothesis that is relevant to the rational and safe use of a drug in humans.

*R. Meyboom et al. 1997*

A signal is reported information on a possible causal relationship between an adverse event and a drug, of which the relationship is unknown or incompletely documented previously.

*Edwards et al. 2000*

# Signal Generation

▶ three convincing ADR-reports

▶ 
$$\frac{\# \text{ specified ADR-Reports}}{\# \text{ Prescriptions}}$$

▶ 
$$\frac{\# \text{ specified ADR-Reports (PRRs)}}{\text{all Reports}}$$

▶ 
$$\frac{\# \text{ specified Reports / Exposed Persons}}{\text{Background Incidence}}$$

# Proportional Reporting Ratio - Example

## Rifabutin and Uveitis

	Rifabutin	all other drugs
Uveitis	41	754
all other ADR	14	591.958
Total	55	592.712

$$\text{PRR} = \frac{586}{55} = 10.6545$$

$$\chi^2 \geq 22.740$$

*S.J.W. Evans et al.: Pharmacoepidemiol Drug Saf 2001;10:483-466*

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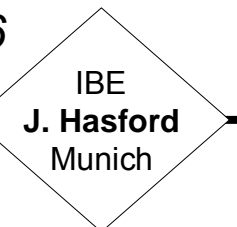
# Proportional Reporting Ratio

	drug of interest	all other drugs in data base
reaction(s) of interest	a	b
all other reactions	c	d
total	a + c	b + d

<p>PRR: <math>a / a+c : b / b+d</math>  PRR = 1: no signal</p>	<p>definition of signals  PRR <math>\geq 2</math>  <math>\chi^2 \geq 4</math>  minimum 3 reports</p>
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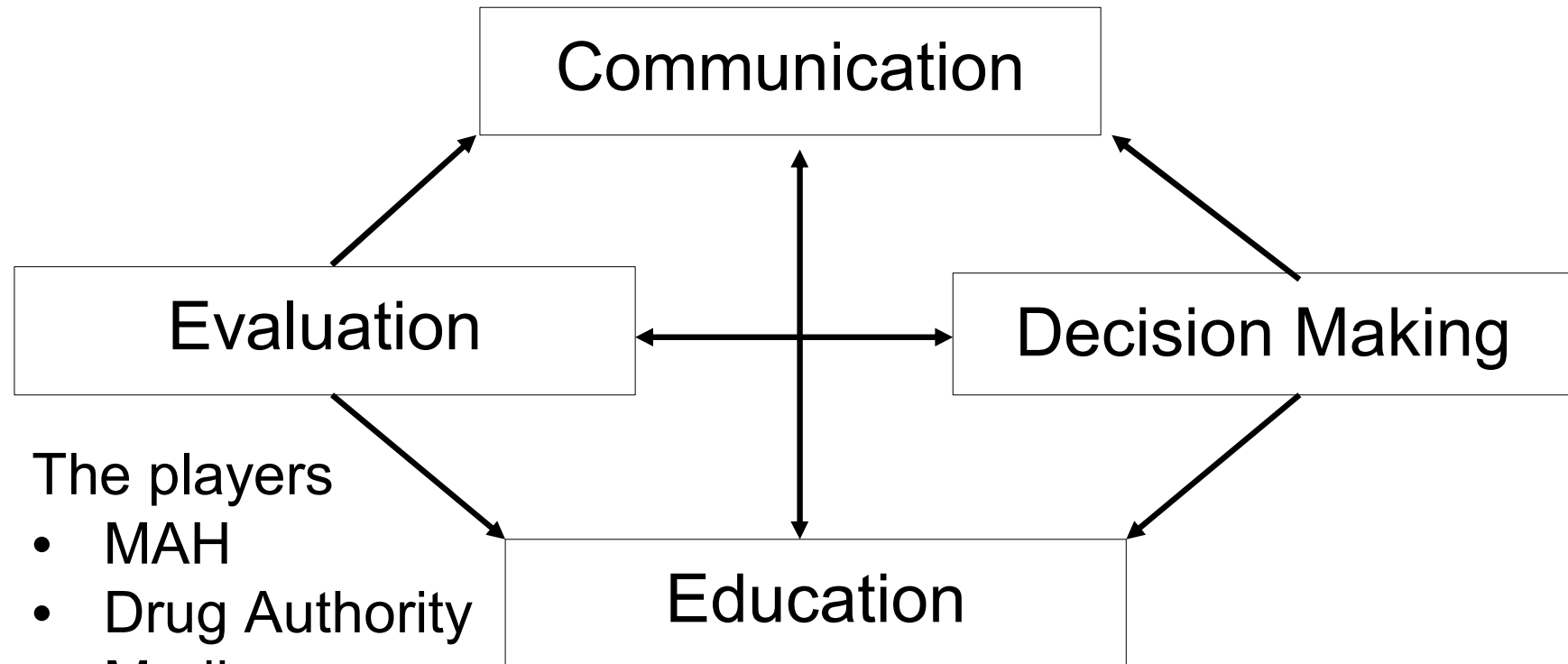
*S.J.W. Evans et al.: Pharmacoepidemiol Drug Saf 2001;10:483-466*



# Proportional Reporting Ratio

- strict causality assessment not essential
- simple, transparent statistics
- no exposure data needed
- only little bias by reporting behaviour
- very strong signals for a particular ADR may hide a less strong signal for another ADR

# Promotion of the Safe Use of Drugs



The players

- MAH
- Drug Authority
- Media
- Physicians
- Patients



# Market Authorization Holder

- ✓ collect, collate, validate and follow up (SAEs) of all reported suspected Adverse Events
- ✓ screen the relevant world-wide literature at least once / week
- ✓ report all serious suspected ADRs within 15 days
- ✓ submit PSURs
- ✓ company-sponsored Post-Authorisation Safety Studies
- ✓ regularly checks risks and benefits and acts accordingly

# Drug Authority

- ✓ collect, validate, code, store and analyse reports
- ✓ transmit ADR data to the MA holder
- ✓ inform health care professionals and, when needed, treated patients, of any significant changes
- ✓ Decision Making
- ✓ Communication with all interested parties
- ✓ Evaluation of the actions taken

## Summary of the Role and the Responsibilities

### Marketing Authorisation Holder

- Establish and maintain a system, accessible at a single point in the EU, to collect, collate, and evaluate pharmacovigilance data
- Meet legal obligations for reporting suspected adverse drug reactions
- Meet legal obligations regarding the preparation and the submission of PSURs
- Respond fully to requests from authorities for additional information necessary for the evaluation of the benefits and risks of a medicinal product
- Ensure the Marketing Authorisation is maintained and reflects the latest information

### Member States

- Have in place national pharmacovigilance systems
- Inform the European Commission, the CPMP, the Agency, the member states and the MAHs of any relevant actions
- Collect and collate risk / benefit data
- Provide serious ADRs which have occurred in its territory to the Agency and the relevant MAH within 15 calendar days of receipt
- Identify and evaluate drug safety alerts and conduct risk / benefit evaluations
- Provide representation on CPMP, PhVWP and Rapporteurs / Co-Rapporteurs
- Implement Commission Decisions
- In case of urgent action to protect public health, suspend the use of the product in the member state's territory and inform, in accordance with the legislation, the Agency and the European Commission of the basis for action

# Public Relations

In all cases it is essential that public relations are handled sensitively and in a timely fashion. Failure to do so may mean that, however well the crisis is managed from a safety and regulatory perspective, public health may be impaired, public confidence will be lost and the image of regulatory agencies and the MA holders will be damaged.

# Pill scare linked to rise in abortions

Abortions in Britain could have risen by up to 10% after the government's warning last year that certain contraceptive pills could increase the risk of deep vein thrombosis.

*BMJ 1996;312:996*

# References and Literature

## **Volume 9 - PHARMACOVIGILANCE**

<http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm>

CIOMS: Reporting Adverse Drug Reactions: Definition of Terms and Criteria for their use

CIOMS: Geneva 1999

### **Journals**

Drug Safety

Pharmacoepidemiology and Drug Safety

### **Society**

International Society of Pharmacovigilance (ISOP)

[www.isoonline.org](http://www.isoonline.org)

