The Need for Pharmacovigilance

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All drugs are dangerous
Some may also be useful

N. Moore, BMJ, 2005, 330;539-40

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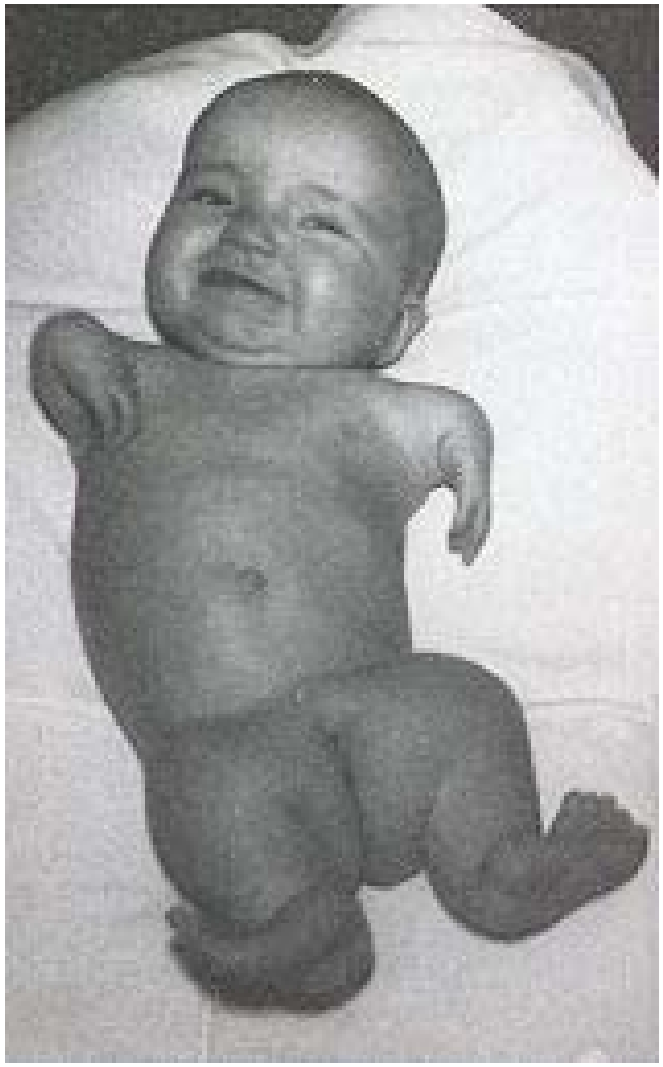
How we woke up



We still need to keep awake!!!!

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Principles of drug therapy not always understood / accepted

- No drug is inherently safe
  - unless it has no effect at all! (i.e. no drug)
- Each patient is unique
- Each treatment situation is unique
  - What is the right drug treatment for me might be a bad choice for you
- Recommendations based on evidence from populations with knowledge of deviations

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WHAT is pharmacovigilance?

WHO definition

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

The importance of pharmacovigilance, WHO, 2002

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Pharmacovigilance is sometimes referred to as

- Drug monitoring
- Drug surveillance
- Post-marketing surveillance
- -
- -

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Extended scope of pharmacovigilance

- Adverse effects (properties of ingredients or patient)
- Patient effects of inadequate product quality (failing GMP, distribution, storage, counterfeiting etc.)
  - e.g. unexpected lack of efficay
- Patient effects of inadequate use
  - medication errors
  - dependence and abuse
  - poisoning
- Safety challenges of mass treatment campaigns
  - immunization programmes
  - other public health programmes

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A shift in focus

- From drug safety to patient safety

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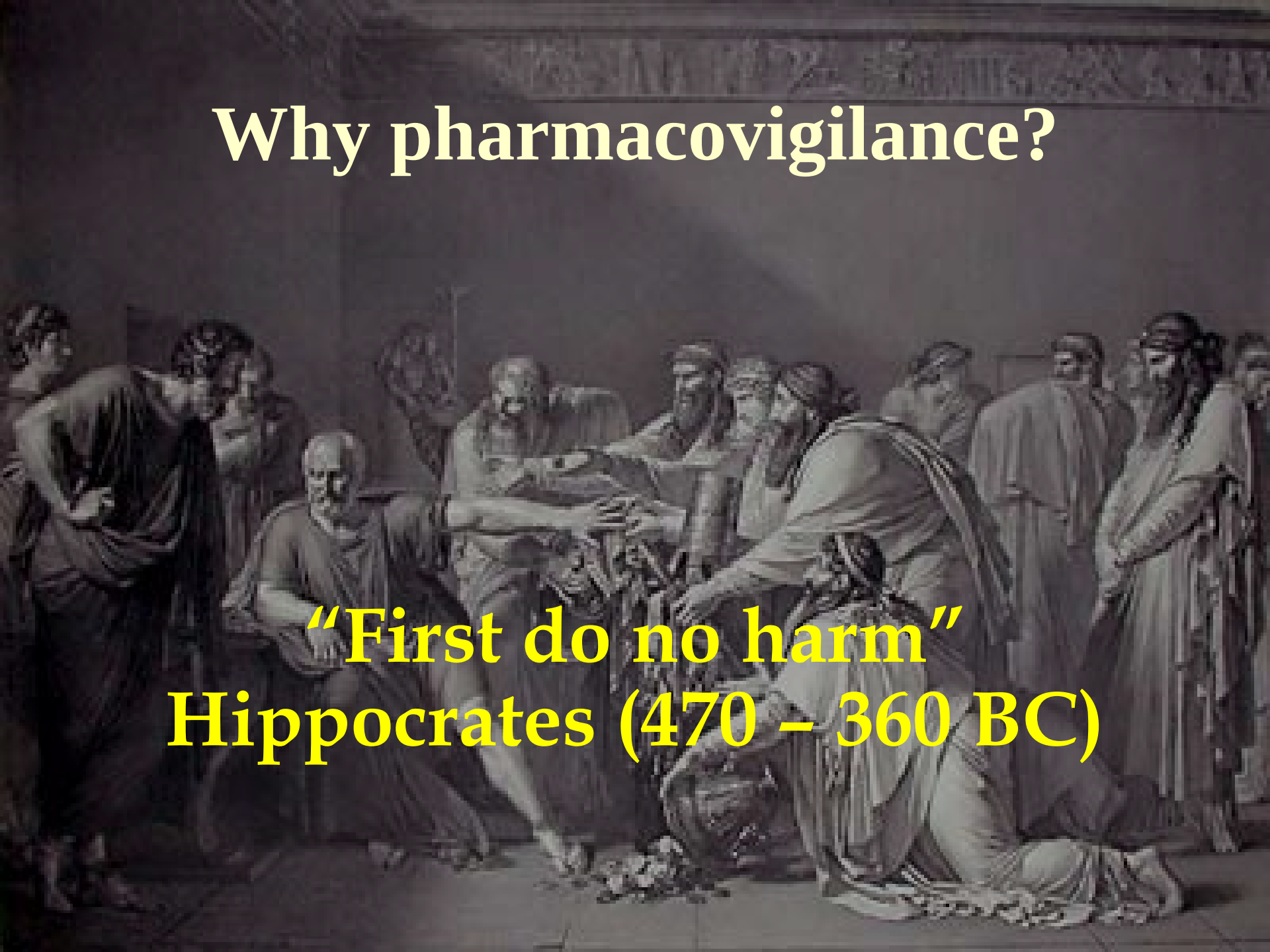
Why pharmacovigilance?



"First do no harm"
Hippocrates (470 – 360 BC)

Why pharmacovigilance?

1. Humanitarian concerns
   Hippocrates' admonition

2. Economic burden to society

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Why pharmacovigilance?

3. Promoting rational use of medicines and adherence

4. Ensuring public confidence

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Safety information before a medicine is put on the market

Experimental studies

- Animal tests
- Clinical trials

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Animal Tests

- acute toxicity
- organ damage
- dose dependence
- metabolism
- kinetics
- carcinogenicity
- mutagenicity
- teratogenicity
- species specificity

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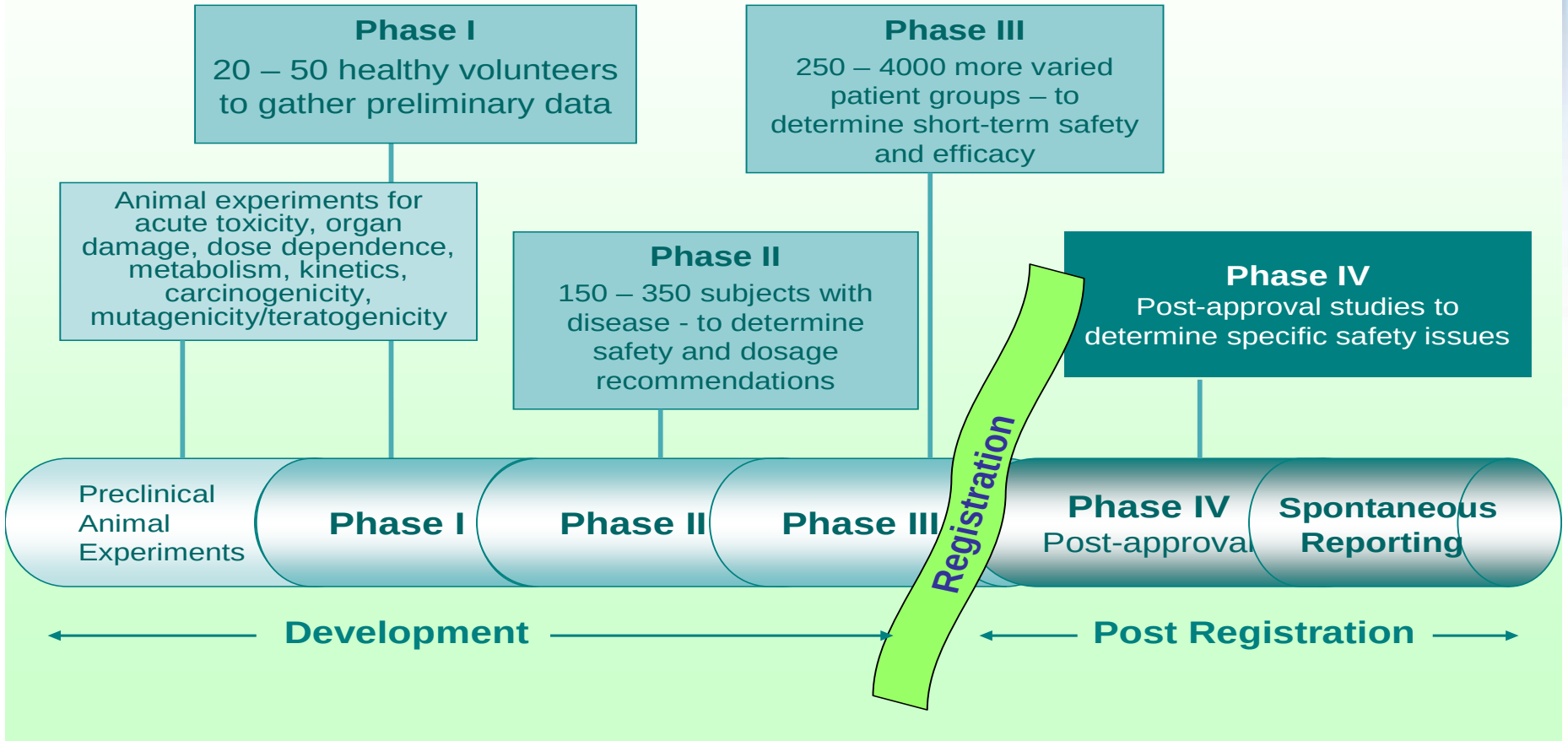
Clinical development of medicines



Rule of 3

- There is 95% chance of observing one occurence of an event in a population 3 times the size of the event's frequency
  - e.g. if the incidence is 1 / 10 000
  - 30 000 patients to find one case

Rule of 3

- Or, if no event is observed in a population of N
- There is a 95% chance that the event rate is less than one in N/3
  - e.g. if there is no event in 3000 patients
  - rate < 1/1000

Why pharmacovigilance?

Limitations of Randomized Clinical Trials (phase 3)

Subject	RCT (efficacy)	Clinical practice (effectiveness)
✓ **Number of patients**	Dozens, hundreds, rarely thousands	Thousands to millions
✓ **Length of time**	Days to weeks	Days to years
✓ **Population**	Pregnant, children, the elderly are excluded	Potentially, all the population
✓ **Other treatments**	They are avoided	Possibly, more than one
✓ **Dose**	Fixed (generally)	Variable (generally)
✓ **Conditions**	Rigorous follow up; more information	Flexible follow up; patient less informed

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Global applicability of results from clinical trials?

International differences

- Genetic
- Social
- Cultural
- Disease prevalence
- Healthcare systems
- Health professional practices
- Indication for, and use of medicines

Effectiveness and risks are not necessarily the same in all populations

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Roles and need for information

Health authority to monitor:

1. Medicines of adequate quality
2. Medicines suitable for intended purpose

   benefit/harm balance
3. Medicines used rationally

   science and experience

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Roles and need for information (2)

Health practitioner

- Each patient a therapeutic challenge

1. Knowledge
2. Therapeutic tools
   - diet
   - surgery
   - medicines
   - etc
3. Knowledge and tools changing
   - need for up-dating

Rational therapy

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Patient

Experience report

Drug Information

Health professional

Communication loops essential

Drug experience report

Drug Information

Drug info/ADR reporting Centre

Health Authority

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Spontaneous ADR reporting

Principle

1. The alert patient/health professional connects an undesirable medical event with drug exposure

A SUSPICION is created

2. Reports suspicion to a pharmacovigilance centre

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Spontaneous reporting systems

- The basis for pharmacovigilance in most countries
- Allows for the collection and systematic analysis of adverse drug reaction reports

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Size and severity of the ADR problem

Meta-analysis- hospital inpatients

- 39 prospective studies from US hospitals
- Overall incidence of serious ADRs = 6.7%
- Overall incidence of fatal ADRs = 0.32%
  (106 000 individuals)
- 4th - 6th leading cause of death

Lazarou et al JAMA 1998;279: 1200 - 1205

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Burden of ADRs
England

- 6.5% of hospital admissions
- 4% of hospital bed capacity
- 0.15% fatality
- 70% avoidable
- Cost to NHS £466 million/year

- Pirmohamed M. et al. Br Med J **329**:15-19 (2004)

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Burden of ADRs

Mumbai, India

- 6.9 % of hospital admissions
- 0.85% fatality
- 60% avoidable
- Additional cost to hospital INR 6197/patient (US$150)

- Patel KJ et al BMC Clin Pharmacol 2007, **7**:8

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Burden of ADRs
Frequently implicated medicines

England	Mumbai
NSAID	Anti-TB
Diuretics	Antiepileptics
Warfarin	Antimalarials
ACE inhibitors	Anticoagulants
Antidepressants	Oral antidiabetics

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US estimate for 2000

- Cost of drug-related morbidity and mortality

>177.4 billion US$

Ref. Ernst & Grizzle J Am Pharm Assoc. 41: 192(2001)

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Burden of ADRs US

- 1.2 million hospitalized patients 2004
  - 90% from proper use
    - 3% of all hospital stays
  - 8.6 % wrong drug, wrong dose
  - Additional cost of $2500/patient

Exilhauser, Owen AHRQ 2007

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Preventable problems

TABLE 2.1

Studies of Preventable Drug-Related Hospital Admissions

Author, Year, Country (reference no.)	Sample Size	DRAs as % of Admissions	PDRAs as % of Admissions	Preventability Rate (%)
Bero et al., 1991, U.S. (4)	224	21.1	15.2	76
Bigby et al., 1987, U.S. (7)	686	10.6	6.3	59
Courtman and Stallings, 1995, Canada (8)	150	14.0	12.0	86
Cunningham et al., 1997, U.K. (9)	1011	5.3	4.3	80
Darchy et al., 1999, France (10)	623	6.6	4.8	73
Dartnell et al., 1996, Australia (11)	965	5.7	3.7	66
Hallas et al., 1992, Denmark (12)	1999	8.0	3.8	47
Lakshmanan et al., 1986, U.S. (13)	834	4.2	2.3	54
Lindley et al., 1992, U.K. (14)	416	6.3	3.1	50
Nelson and Talbert, 1996, U.S. (15)	450	16.2	9.5	59
Ng, et al., 1999, Australia (16)	172	18.0	5.8	32
Nikolaus et al., 1992, Germany (17)	87	25.3	12.6	50
Raschetti et al., 1997, Italy (18)	1833	2.5	1.4	56
Trunet et al., 1980, France (19)	325	7.1	4.3	61
Trunet et al., 1986, France (20)	1651	5.9	2.6	44
Median	623	7.1	4.3	59
Minimum	87	2.5	1.4	32
Maximum	1999	25.3	15.2	86

Source: Winterstein et al., *Ann. Pharmacother.*, 36, 1238, 2002.

LA
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Ethics in pharmacovigilance

The small girl allegory

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Ethics in pharmacovigilance

- To know of something that is harmful to another person who does not know, and not telling, is unethical

Modifiers

- knowledge - suspicion
- if other person should have known
- seriousness
- distance ????

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Consequence

- Not reporting a serious unknown reaction is unethical

valid for everyone

- patient
- health professional
- manufacturer
- authorities

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Pharmacovigilance
Major Aims

- early detection of unknown safety problems
- detection of increases in frequency
- identification of risk factors
- quantifying risks
- preventing patients from being affected unnecessarily

Rational and Safe use of Medicines

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Thank you for your attention

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