



The Challenges of Pharmacovigilance

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"Courage is the human virtue that counts most—courage to act on limited knowledge and insufficient evidence. That's all any of us have."

~ Robert Frost

20th century American poet and three time
Pulitzer prize winner (1924, 1931, 1937)

The problem

(all **red text** indicates need for improvement)



Size and severity of the ADR problem

Patient safety signals.

- 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



6.7% of hospital patients have serious adverse drug reactions (medication error excluded)

Lazarou J, Pomeranz BH, Corey PN. JAMA 1998;279:1200-5

16.2% of hospital admissions are drug-related

Therapeutic failure 54.8%

Adverse reactions 32.9%

Overdose 12.3%

Avoidable 49.3%

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



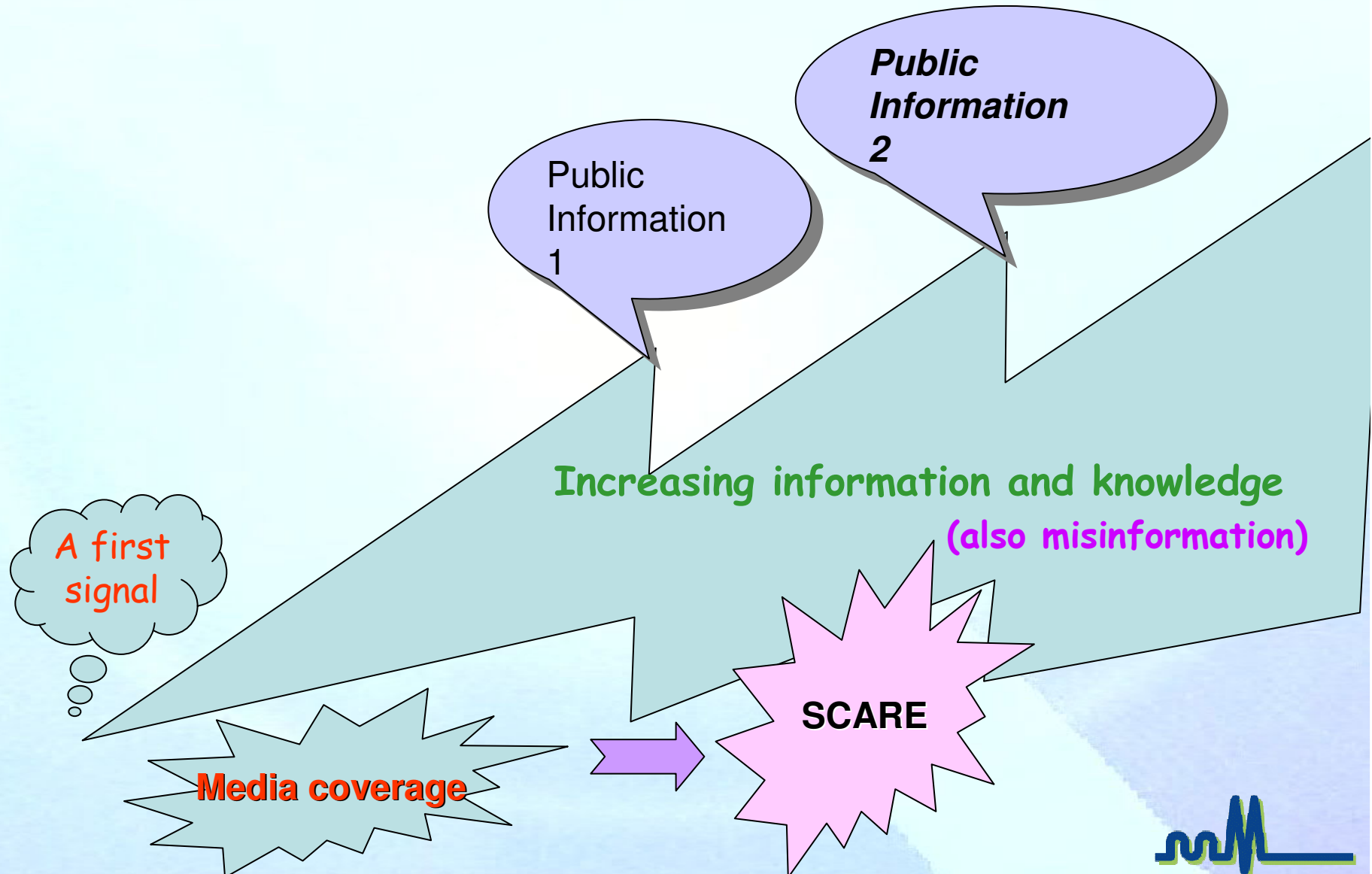
Pirmohamed M JS, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.

BMJ 2004;329(7456):15-19.

-identifies the main drug culprits in a large hospital based study. They are old drug groups (low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs other than aspirin: the most common reaction being gastrointestinal bleeding) on which we have much information.....



Managing a signal ?



Five broad activities essential to pharmacovigilance:

- Suspected ADR signal detection and formation of hypotheses
- Analysis of all issues around the signal, particularly confirmation (or refutation) of hypothesis, estimation of the size of the risk and whether susceptible patients exist
- Consideration of possible effectiveness-to-risk issues in therapy (comparative)
 - How to do it?
 - Economics
- Communication of information to health professionals and patients in a useful way. And possible regulatory action.
- Consequence evaluation.

Decisions

Decisions

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Decisions



Problems of withdrawal & regulation (examples)

Consequences - Outcomes research needed



Examples

- Slow action
- Precipitate action
 - Lack of evidence
- Influence of media
- Complexity
- Effectiveness & risk
 - Confusion
- Pseudo-safety withdrawals
 - Company finances
- Cisapride, Digesic
- Many old examples
 - also Sertindole
- Many eg. Vioxx
- COX2 & NSAIDS
- Phenylpropanolamine
 - Dose and indication
- Nefazodone
 - monitoring



Examples

- Off-label usage
 - Dosage
 - Failures of guidance
- Long term effects
- Pre-marketing information suppressed
- Scientific confusion
- Herbals safety
- Vioxx (dose)
 - Cerivastatin (int-act)
 - Troglitazone (monit)
- HRT (breast ca.)
- SSRI
 - Company problem, not drug?
- HRT (heart dis. or ?)
- Aristolochia
 - Species?



Example of a decision problem to be solved [1] ...

Cisapride - heart rhythm disorders

- 1986: double blind study "cisapride produced tachycardia"
- 1992 WHO Signal published in Br Med J on serious arrhythmia
 - letters to Br Med J "no epidemiological support"
- 1995 case report published, Lancet "QT prolongation and tachycardia"

Dear Doctor letter in USA by manufacturer

Should cisapride still be marketed?



Example of a decision problem to be solved [2] ...

- Piroxicam is the most GI toxic of the NSAIDS in several comparative studies
 - GI toxicity is a major cause of morbidity

Should piroxicam replace rofecoxib in Venezuela?



Discussion points

How often is drug withdrawal really necessary?
Does withdrawal harm people that it helps?
Does withdrawal have the same signal to useful, and properly used, information



Visions and goals of patient/drug safety

Prevention in drug safety

Effectiveness and risk

Need for comparison between medicines

Risk assessment



The true balanced concepts

- Efficacy (hard data)
 - Effectiveness
 - Benefit (what the patient feels)
 - Hazard
 - Risk
 - Harm (soft data)
-
- The diagram illustrates the relationship between these concepts. A green arrow labeled "Yes!" points from "Benefit (what the patient feels)" to "Harm (soft data)". A pink arrow labeled "NO!" points from "Efficacy (hard data)" to "Risk".

This does matter



Goals and tools

- Problems with medicines
 - Find them
 - Causation
 - Analyse them
 - Put them in context
 - Quantify them
 - Effectiveness and risk
 - Comparisons
- Spontaneous reports
 - Data mining
 - Epidemiology
 - Careful assessment of all relevant data
 - How? Who?



Goals and tools

- Problems with medicines
 - Prevent or limit them
 - Manage them
 - Maximise effectiveness with minimum risk to *individual patients*
- Offer best treatment options
 - Most effective
 - Safest
 - Cheapest
- Check result
- Risk management
- Communicate information to HPs & patients
- Check for response
- Communicate to the health authorities, public & others
- Check media: surveys



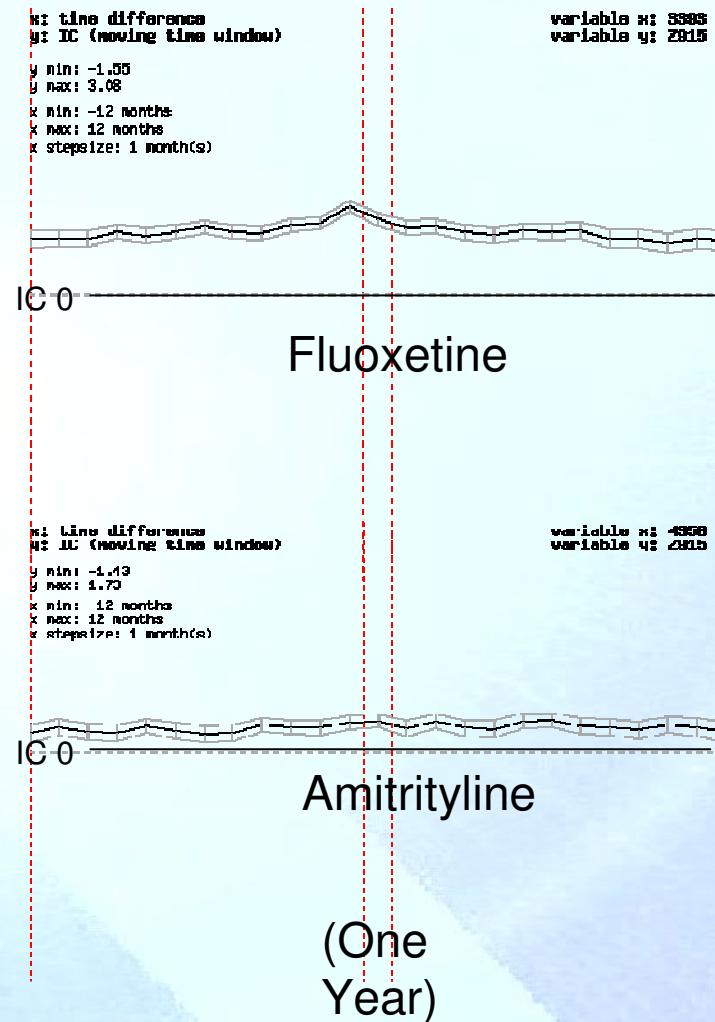
Do we really use our tools?

- Case reports *can* tell us a huge amount about what concerns individual doctors/h.p's/consumers
 - We could get much more information on what happens to people, medication error, interactions, patients at risk, how to diagnose ADRs, etc.
- Studies tell us about populations and not individuals
 - Many important ADRs are rare ($< 1/1000$)
 - Large numbers of exposed patients and controls needed
 - We need more, and much better, ways of using health service databases



Measuring true effectiveness and risk with SSRIs?

- Needs knowledge finding in patient care databases
 - E.g Data mining in IMS Health database of 2 million patients
- Can show comparative effectiveness and risk
 - Data quality



Suicidality



*A new look at spontaneous
reports*

**Reports of concerns about
therapy**

Client dissatisfaction reports



Reports of concerns about therapy

- **Novel drug signals** (traditional pharmacovigilance)
 - Careful clinical evaluation of all the clinical circumstances a differential diagnosis, or causal potential, for that individual.

A serious misconception is, however, that these reports are poor epidemiology.



Novel drug signals

- E.g. The conversion of cases into database epidemiological data has cost us time in recognizing
 - the SSRI 'electric shock' syndrome (entered into databases as 'dysaesthesia',
 - the sumatriptan 'pain reactivation syndrome' (Coulter DM, Passier JL, Clark DW, van Puijenbroek EP. Activation of pain by sumatriptan. *Headache*. 2003 Oct;43(9):994-9.),
 - statin caused rhabdomyolysis (first recorded in databases as 'myopathy').



Reports of concerns about therapy

- **Patient safety signals.**
 - Because pharmacovigilance experts may know about a particular drug/ADR relationship does not mean that everyone knows or uses that information.
 - There may be need for other action: mainly communication/education



Patient safety signals.

- Continued high levels of reporting of 'known' ADRs should lead to an informative newsletter and also individual helpful responses e.g.
 - Some known ADRs may be reported because they are different in quality than expected (e.g. more severe).
 - A particularly severe skin rash with amoxicillin may be due to undiagnosed immune disorders. A response suggesting that might be helpful.
- Drug interactions are often not diagnosed
 - a response to a report on a common dose related ADR might suggest the possibility.



Patient safety signals.

- ADRs following contraindicated drug use
 - Beta-blocking drugs causing severe (asthma) should be followed by a very firm, but not judgemental, reply: ethical standards demand that.
- Continued large numbers of reports of known associations should result in an educational article in a local journal or newsletter.
 - Benzodiazepine dependence



Reports of concerns about therapy

- **System signals**
 - Much criticism is made of spontaneous reporting defects, but not much intelligent use is made of information that would lead to improvements.



System signals

- Knowledge that general practitioner reports are much greater than hospital reports should lead to a campaign to improve the latter.
- Low reporting in some therapeutic areas should suggest the same need for attention to those areas.
- Poor quality of reports should lead to education. This may be individual, supportive feedback or general via newsletters



Other needs

- There are much more active approaches needed for education of HPs and public in all countries
 - more pro-active use of the media
 - much more interest in patient safety issues
 - Medication errors
 - Root -cause analysis
- There is a great need to know the basis for regulatory decisions
 - particularly those made in the developed world



Patient involvement

- Patients need more general information about drugs and their effectiveness and risk
- **VERY IMPORTANT**
 - We need much more information about what risks patients are prepared to take for what benefit to them. Until we know this we will continue to 'second-guess' about what is acceptable or not



Managing a signal: the future

What do HPs and patients think and want

Public Information 2

Public Information 1

A first signal

Increasing information and knowledge

Pre-marketing risk management

Media coverage



Conclusions

- Think less about drug safety: more about patient safety
 - Use and react to concerns
- Think less about regulating (incl. withdrawal) and automating data input: more about useful information output
- Think more about impact and consequences of decisions and non-decisions



Conclusions

- ‘...Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs...’
- Erice Declaration, 1998.

