

Benefit-harm assessment

Effectiveness-risk assessment

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UMC Pharmacovigilance Training Course
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Kind acknowledgements to Ralph Edwards

Aims of PV course

To provide a foundation of knowledge and understanding of the core principles and best practice standards in pharmacovigilance

- **Discuss concepts, principles, and methods in benefit-harm assessment**



Background

- All drugs come with a risk of side effects
- How do we determine whether these risks are too great?
 - Whether the “benefit-risk balance is positive”
- Straightforward question (?) without a straightforward answer
- Aim is to give an insight into the many aspects of this problem



A confusion of concepts

- Terms used to describe positive aspects of drug treatment:
 - Benefit
 - Effectiveness
 - Efficacy
- Terms used to describe negative aspects:
 - Harm
 - Risk
 - Hazard

What are the differences?



Benefit and its opposite harm

- We are interested in benefit and harm at the individual level
 - What a patient experiences
- Benefit
 - "Something that contributes to or increases one's wellbeing"
 - Example: Cure hyperthyroidism by surgery
- Harm
 - Example:
 - Hypothyroidism caused by surgery
 - Symptomatic agranulocytosis caused by antithyroid drugs



Benefit vs effectiveness and harm vs risk

- Effectiveness
 - Relates both to the probability and the "magnitude" of beneficial effect
 - Indicates to what extent the drug works in the population, in normal clinical use
- Risk
 - Relates to probability (incidence) and "impact" of certain harmful effect
- Effectiveness and risk are measured in the population; cannot be measured on single patient
 - Benefit and harm, on the other hand, are what the patient experiences



The balanced concepts

- And where to find data -

- Efficacy vs hazard
 - Pre-clinical / clinical studies
- Effectiveness vs risk
 - Spontaneous reports
 - Post-marketing clinical use studies
 - Healthcare databases / registries
- Benefit vs harm: What is actually experienced by a patient or group of patients
 - Spontaneous reports



What variables can we use to balance effectiveness and risk?

- Are they different than those we might use to balance benefit and harm?
- *How* do we balance both sides of the equation?



Three key dimensions

Edwards et al., 1996

- **Seriousness**
 - Of ADRs
 - Of disease (treated and untreated)
- **Duration**
 - Of ADRs
 - Of disease
 - Of beneficial effects
- **Frequency (incidence)**
 - Of ADRs
 - Of disease
 - Of successful treatment



Description of key dimensions

	High	Medium	Low
Seriousness	Fatal	Disabling	Inconvenient
Duration	Permanent	Persistent	Temporary
Incidence	Common	Infrequent	Rare

- Remember: This applies to the disease being treated, how the drug alters the disease, and any ADRs
- Can be quantified

Example: Efalizumab / natalizumab and PML

- Two mechanistically similar drugs, with same main safety concern (Progressive multifocal leukoencephalopathy: PML)
 - Very infrequent, but very serious (often lethal)
- Natalizumab (Tysabri) used as last line MS treatment
 - Quite serious disease, at least in a part of cases
 - Decision: Use in subgroups; monitor safety
- Efalizumab (Raptiva) used as last line psoriasis treatment
 - Inconvenient, but not usually serious disease
 - Decision: Withdraw from market

Comments?



Absolute or relative?

- Can we assess the effectiveness-risk of a drug (for a certain indication) without considering alternative therapies?
- Most likely not: If two drugs are equally effective and both have acceptable but different risk profiles, we will choose the one with the more favourable risk profile
 - However, recall efalizumab: Not even granted use as last line treatment, i.e. risks considered to outweigh effectiveness *absolutely*

Is that right?



From principles to method

- We know what aspects to consider, so what is the problem?



From principles to method

- What is the relative importance of frequency, seriousness, and duration?
 - Typical example: Detection of rare but serious ADR for an effective drug in mildly serious disease
 - Detrimental harm to a handful versus moderate benefit to thousands (or even hundred of thousands)
- What data?
 - The different types of data can be *very* different
 - Animal studies, clinical randomized studies, clinical observational studies, healthcare databases, quality-of-life studies, spontaneous reports...
 - How do we weigh an estimated efficacy of 60% in an RCT against five spontaneous reports?



Example: alosetron

- Indicated for women with severe diarrhoea-prominent IBS
- Taken off the market 2000 because of serious complications (constipation, ischaemic colitis), then reinstated again 2002
- What do we know about the 'key dimensions', and from what data sources has this information been gathered?



Alosetron

	IBS untreated	IBS treated	Complications (only serious)
Seriousness	'inconvenient'? 'disabling'?	'adequate relief' (clinical trials)	Some requiring hospitalisation and surgery; some even fatal (spontaneous reports)
Duration	'persistent'? (<i>varying</i>)	12 weeks? 6 months? (<i>varying</i>)	Temporary-permanent (<i>varying</i>)
Incidence	'common'	Adequate relief in 42% vs 28% with standard care (clinical trials)	'rare' About 3/1000 in total About 1/50 of those lethal (clinical trials + spontaneous reports)

Alosetron

- Fundamental questions:
 - Is it ever worth treating a non-lethal condition with a drug that could cause lethal complications?
 - If so, when? What about this case?
 - What to do with all the uncertainty and the mixing of data sources?
- Conclusion: Even if we know what dimensions that are relevant to the problem, there is no straightforward way to come up with a solution.



From principles to method

- Population or individual? (Cf. Effectiveness-risk or benefit-harm)
 - Population: e.g. a regulatory decision
 - Individual: e.g. the choice of therapy for a certain patient
 - A certain individual might be willing to live with the risk of a serious side effect if the benefit to that individual is large enough
 - *"I'd rather die dry than live in a wet hell."*
 - Real quote from 90-year old woman after terodiline withdrawal
 - Different individuals might *perceive* risks differently



What else should be considered?

- Is there uncertain causality around any effects?
 - E.g. an emerging safety signal
- How are risks perceived?
 - In general
 - In individual patients
- Value judgements



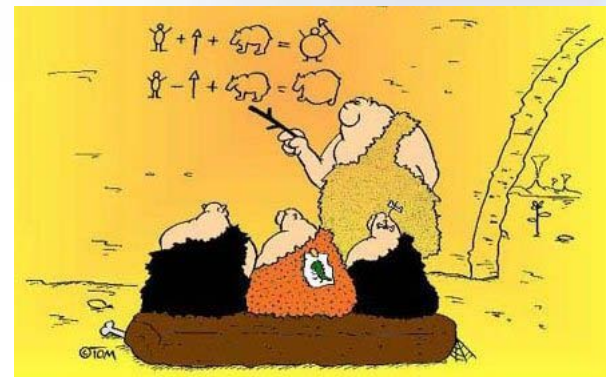
... and more ...

- Drug interactions?
- Compliance?
 - E.g. due to late onset of benefits
- Risk of improper use?
 - E.g. abuse
- Important differences between patient subgroups?



Qualitative, semi-quantitative, or quantitative?

- Can we put numbers on all of this?
- A matter of scientific debate
- CHMP working group on benefit-risk assessment methods (2008):
 - *“Expert judgment is expected to remain the cornerstone of benefit-risk evaluation for the authorisation of medicinal products. Quantitative benefit-risk assessment is not expected to replace qualitative evaluation.”*
- However, this might be changing...



An ideal method should...

- ... take into account both frequency and 'magnitude' (duration and seriousness)
- ... consider multiple effects, i.e. several ADRs
- ... be able to assess a single drug or compare many drugs
- ... consider all data sources
- ... allow for uncertainty
- ... be applicable to population or individual, as needed

*UMC has such a method in its
pilot phase*



An ideal method should...

- ... be transparent!



Older methods, examples

- Number-needed-to-treat (NNT) and number-needed-to-harm (NNH) (Laupacis et al., 1988; Mancini et al., 1999)
 - Single beneficial effect, single adverse effect
 - Mainly useful for single RCT
- "Principle of Threes" (Edwards et al., 1996)
 - Three dimensions (seriousness, frequency, duration)
 - Disease, effect of drug on disease, adverse effects
 - Three most common and three most serious adverse effects



More complex methods, examples

- Based on decision analysis (e.g. Mussen et al., 2007; Felli et al., 2009)
 - Mostly criteria-based: Define hierarchy of relevant criteria; assess relative importance of these criteria; and score the different drugs on the criteria
- Based on statistical modelling
 - "Global" models (e.g. Sutton et al., 2005)
 - Patient-based simulations (e.g. van Staa et al., 2008)



... and the winner is?

- No method yet has gained wide-spread use
 - Academic world
 - Regulatory world
- CIOMS IV report, 1998:
 - *"It is a frustrating aspect of benefit-risk evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data and that might permit straightforward quantitative comparisons of different treatment options, which in turn might aid in decision making."*

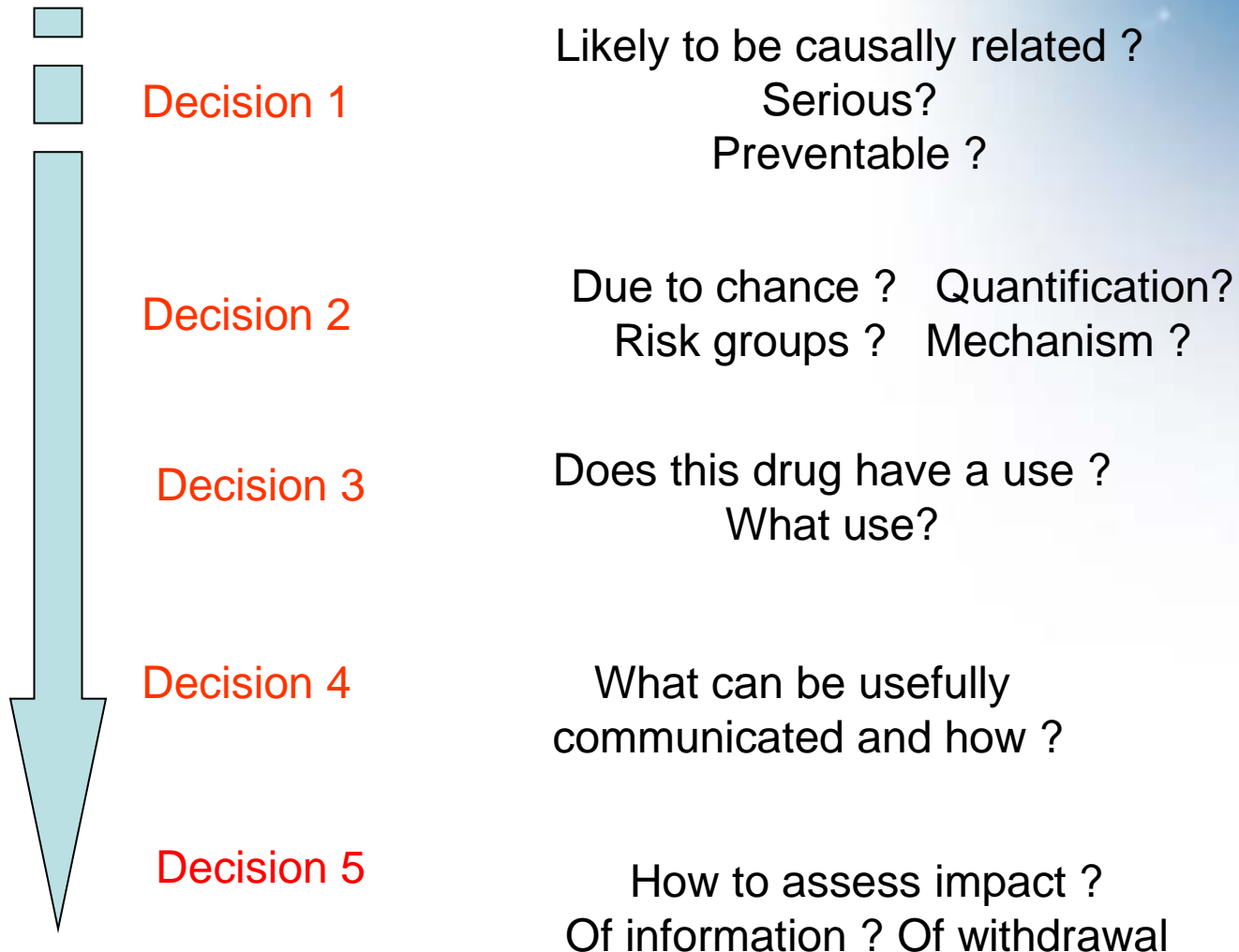


A broader pharmacovigilance outlook

- Suspected ADR signal detection and formation of hypotheses of the size of the risk and whether susceptible patients exist
Decision 1
- Analysis of all issues around the signal, particularly confirmation (or refutation) of hypothesis, estimation
Decision 2
- Consideration of possible effectiveness-to-risk issues in therapy (comparative)
 - How to do it?
 - EconomicsDecision 3
- Communication of information to health professionals and patients in a useful way. And possible regulatory action.
Decision 4
- Consequence evaluation.
Decision 5



Five broad activities essential to pharmacovigilance:



Decisions are made – with or without methods!

- A new drug application must be approved – or not
- A new safety concern must be acted upon – or not
 - Spontaneous reports have a substantial impact (e.g. Clarke et al., 2006; Olivier et al., 2006)
- Individual therapy decisions must be made
 - No treatment is also a choice!
- Lack of good methods implies
 - Less transparency
 - Less consistency
 - Worse communication



Communication

- "The correct message to the right audience by the right medium"
- Information on the "safety" (often risk) of medicines should be in context
 - With effectiveness
 - Compared to other alternatives (Cf. Vioxx)
 - In time and place
- Good communication promotes
 - Appropriate action by health professionals
 - Appropriate action by patients



Summary and conclusions I

- Concepts with different meaning should not be confused
- Effectiveness and risk evidence selects probable best therapies
 - For policy decisions
 - And guide use in individual patients
- Clinical assessments of benefit and harm experience fine tune selection decisions
 - In individual patients
 - And contribute qualitative information to policy decisions
- Both risk and effectiveness can be captured in terms of seriousness, frequency, and duration



Summary and conclusions II

- Benefit-harm / effectiveness-risk assessments currently rely on expert judgement
 - More formal methods require development and time to mature
- Decisions are made with or without formal methods
- Communication is a key aspect



References I

- Edwards IR, Wiholm B-E, Martinez C. Concepts in Risk-Benefit Assessment. *Drug Safety*, 1996; 15(1): 1-7.
- www.emea.europa.eu/humandocs/Humans/EPAR/raptiva/raptiva.htm
- www.emea.europa.eu/humandocs/Humans/EPAR/tysabri/tysabri.htm
- www.emea.europa.eu/pdfs/human/brmethods/1540407enfin.pdf
- Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine*, 1988; 318(26): 1728-1733.
- Mancini G, Schulzer M. Reporting Risks and Benefits of Therapy by Use of the Concepts of Unqualified Success and Unmitigated Failure. *Circulation*, 1999; 99: 377-383.



References II

- Mussen F, Salek S, Walker, S. A quantitative approach to benefit-risk assessment of medicines - part 1: the development of a new model using multi-criteria decision analysis. *Pharmacoepidemiology and Drug Safety*, 2007; 16(S1): S2-S15.
- Felli JC, Noel RA, Cavazzoni, PA. A Multiattribute Model for Evaluating the Benefit-Risk Profiles of Treatment Alternatives. *Medical Decision Making*, 2009; 29(1): 104-115.
- Sutton A, Cooper N, Abrams K, Lambert P, Jones D. A Bayesian approach to evaluating net clinical benefit allowed for parameter uncertainty. *Journal of Clinical Epidemiology*, 2005; 58(1): 26-40.
- van Staa TP, Cooper C, Barlow D, Leufkens HG. Menopause. 2008 Mar-Apr;15(2):374-81. Individualizing the risks and benefits of postmenopausal hormone therapy. *Menopause*, 2008; 15(2): 374-381.



References III

- Working CIOMS Group IV. Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. CIOMS: Geneva, 1998.
- Clarke A, Deeks JJ, Shakir SAW. An assessment of the publicly disseminated evidence of safety used in decisions to withdraw medicinal products from the UK and US markets. *Drug Safety*, 2006; 29(2): 175-181.
- Olivier P, Montastruc JL. The nature of the scientific evidence leading to drug withdrawals for pharmacovigilance reasons in France. *Pharmacoepidemiology and Drug Safety*, 2006; 15(11): 808-812.

