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Benefit-risk assessment throughout the drug lifecycle: future challenges?

PCWP & HCPWP workshop
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An agency of the European Union

Anatomy of benefit-risk assessment

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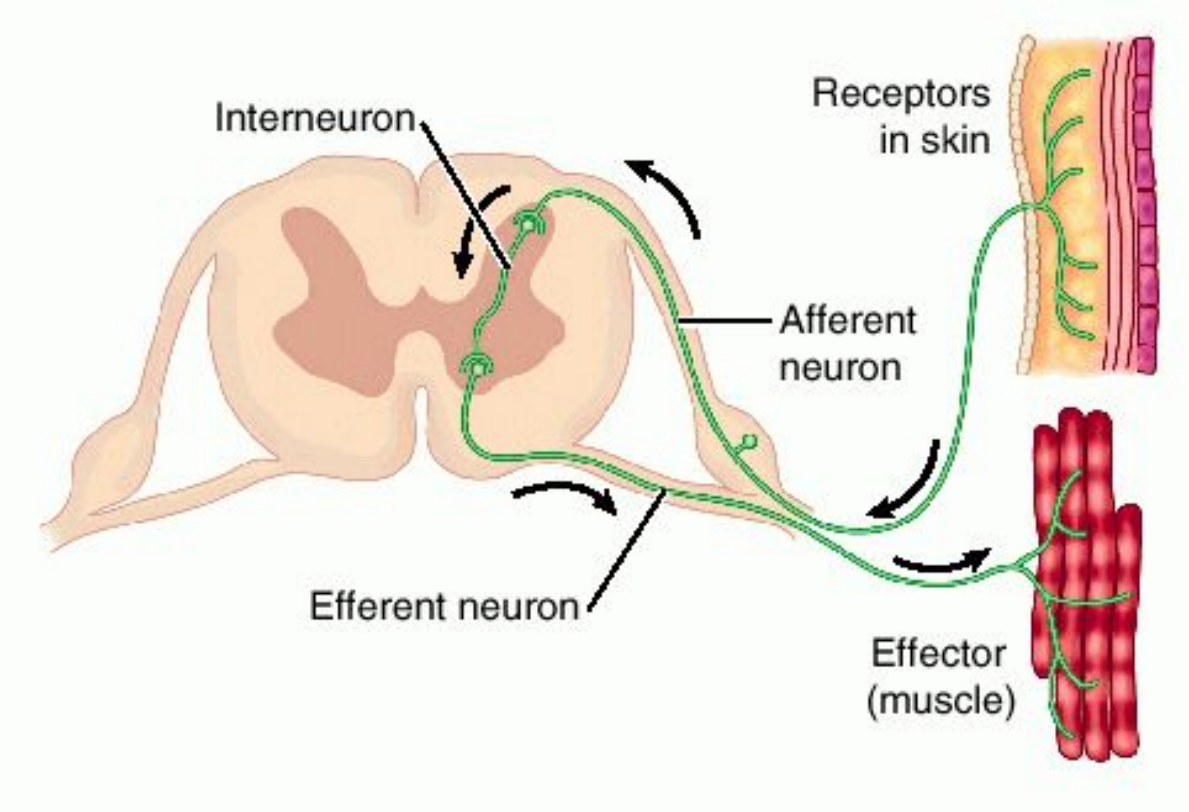

- Incoming signals
- Information processing
- Outgoing (re-)action

Agenda

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- Incoming signals
  - Noise, signals, data, information
- Information processing
  - Facts, values, uncertainty, risk aversion
- Outgoing (re-)action
  - Communication, modifying human behaviour

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What comes in?

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Sources of *data:*

- randomised controlled trials
- uncontrolled clinical trials
- spontaneous adverse event reports
    - registries
    - observational studies (in many forms and shapes)
    - N-of-1 trials
    - pragmatic clinical trials
    - networks, e.g. ‘patientslikeme’ type data
    - digital social media, apps
    - anecdotes, media reports

Speaking of noise…

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False positive signals: 2009-12, EMA reviewed 7557 potential drug safety problems; ~1/40 → further investigation; 1/157 → label changes

[Koenig F, Slattery J, et al. Biometrical J 2013, in press]

What is signal - what is noise? What information should go into the benefit-risk evaluation?

‘Hierarchy’ of evidence and regulatory decision making

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Ia: systematic review or meta-analysis of RCT’s

Ib: at least one RCT

IIa: at least one well-designed controlled study without randomisation

IIb: at least one well-designed quasi-experimental study, such as a cohort study

III: non-experimental descriptive studies, e.g. comparative studies, correlation studies, case–control studies and case series

IV: expert committee reports, opinions and/or clinical experience of respected authorities

PROTECT

Methods used to address data heterogeneity

RCT vs. observational data:

- Use Bayesian mixed treatment analysis (MTC) quantifying inter-study variability and heterogeneity
- Use study level covariate to reflect the design and evaluate e.g. under-reporting of risk outcomes
- Perform sensitivity analyses

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What is expected from a regulator?

"[…] Decisions in healthcare are rife with moral disagreements" →

unanimity is an elusive goal

Accountability for reasonableness* :

- Transparency
- Relevance
- Revisability

*Daniels N et al. Accountability for reasonableness: an update. BMJ 2008;337:a1850

Would a structured decision framework:

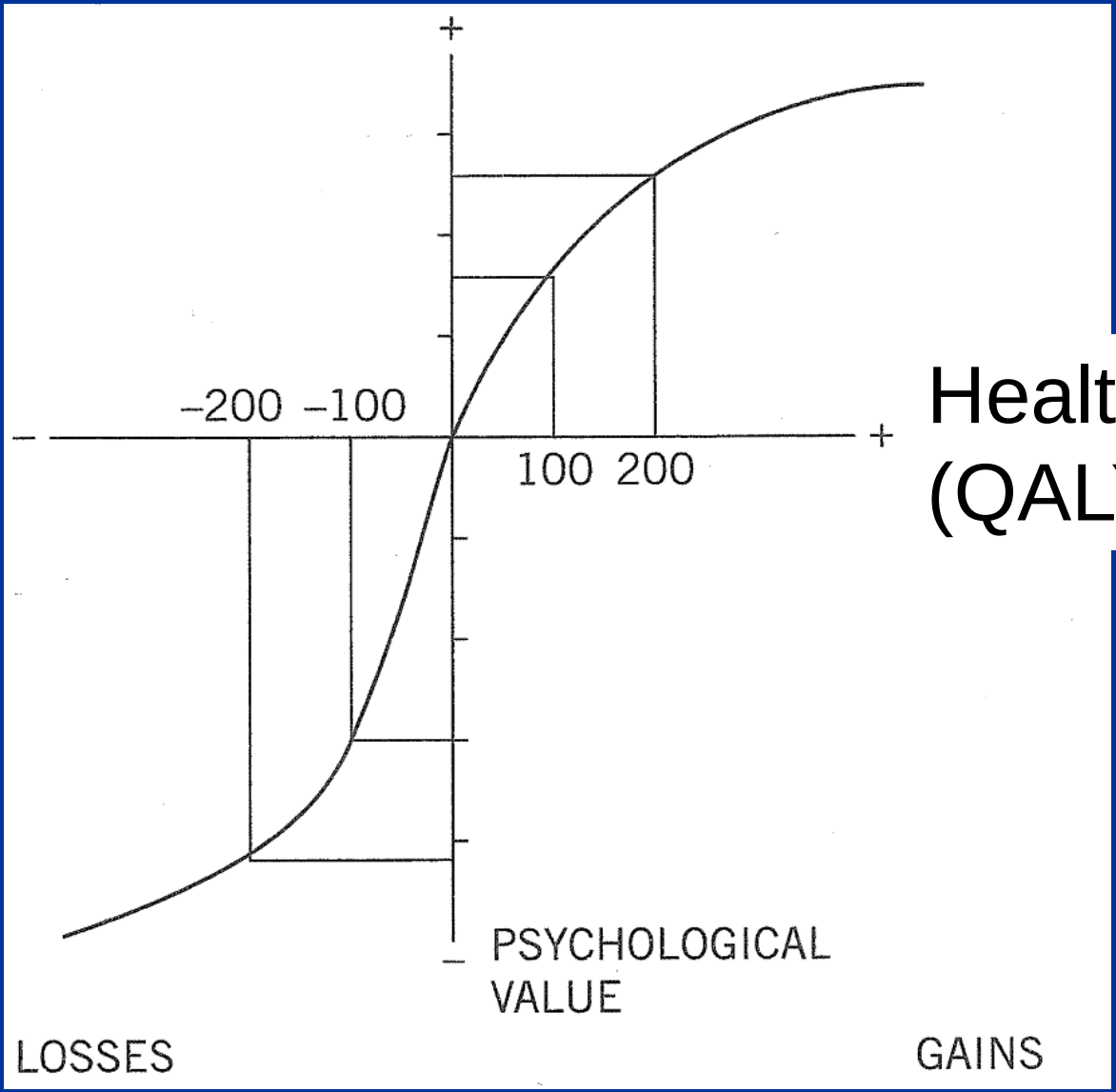
- add transparency and relevance?
- affect the outcome of the decision?

The regulators' decision-rule:

- do the benefits outweigh the risks?
- is the degree of uncertainty around B & R acceptably low?

B - H - U (benefits, harms, uncertainty)

Loss (Risk?) aversion



Health
(QALY, DALY, LYS)

Kahneman D. Thinking, Fast and Slow.
London, Penguin Books, 2011

The asymmetry of benefit-risk

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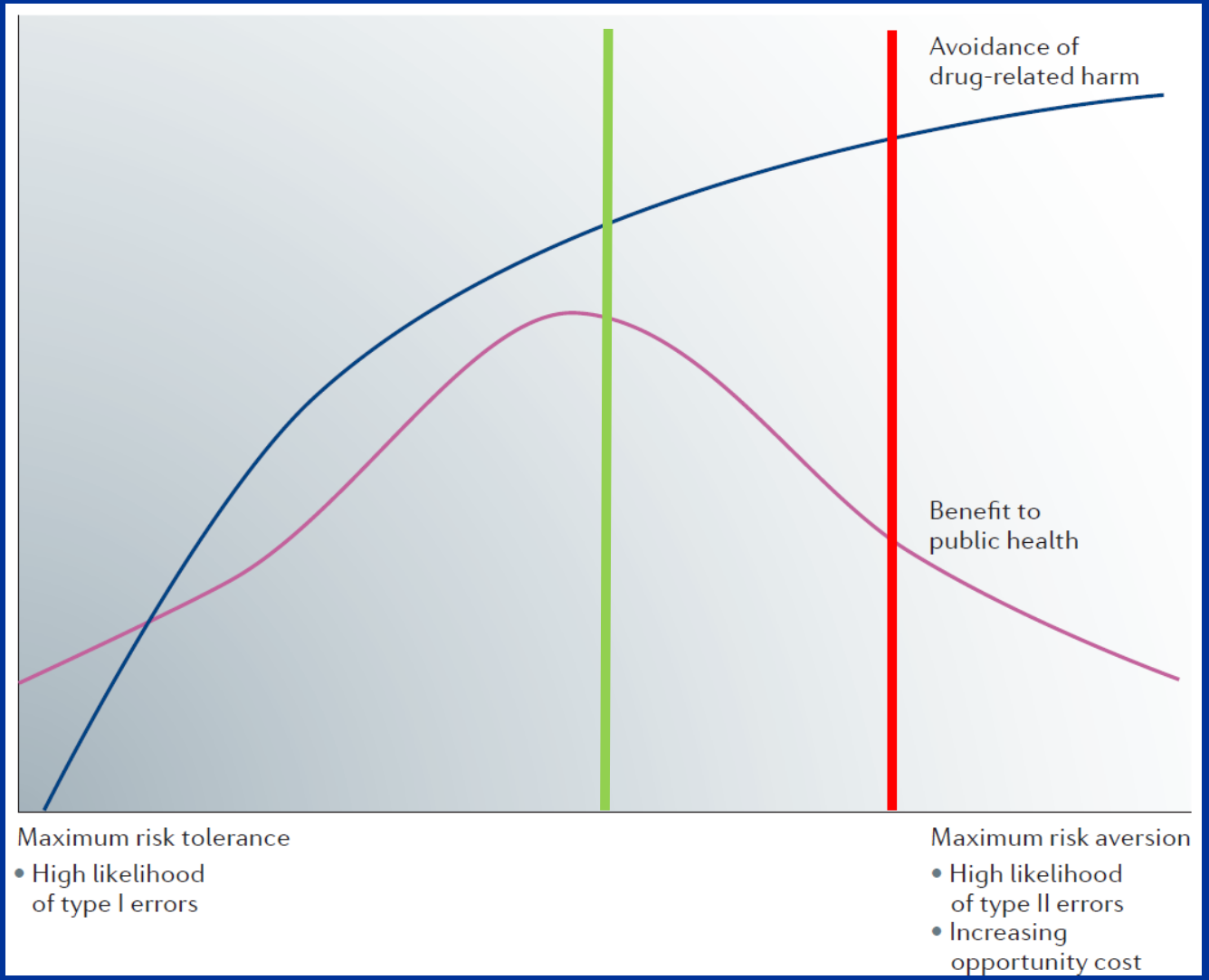
Survey of value judgments among practicing hospital physicians:

on average, ‘four or five additional lives had to be saved by better treatment of the disease for each additional death caused by the treatment itself.’

→ most physicians view death attributable to disease as a more acceptable outcome than death attributable to iatrogenesis.

Lenert LA, et al: Primum non nocere? Valuing of the risk of drug toxicity in therapeutic decision making. Clin Pharmacol Ther. 1993; 53(3):285

Would patient involvement or different framing change anything?



Eichler et al. The risks of risk aversion.
Nature Rev Drug Disc 2013, Dec;12(12):907-16

A structured benefit-risk framework:

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- will likely add clarity and transparency, perhaps improve the ‘light to heat ratio’ in public debate
- may require patient and health care professionals involvement and judicious framing: benefit-risk or risk-risk trade-offs ?
- may expose B-R asymmetry → influence the decision?

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Case study: Acomplia
(rimonabant 20 mg)

Jun 2006: approved for obesity and over-weight patients.

("effect was moderate and of clinical relevance for 20-30% of patients")

Case study: Acomplia
(rimonabant 20 mg)

Jan 2009: marketing authorisation withdrawn in light of post-approval data

("new data indicated a shorter duration of treatment in real life and a reduced beneficial effect…

risk of experiencing the adverse mental effects are higher in patients with comorbidity")

Utilisation, adherence, can/should regulators contribute?

- better communication?
- better support of technology?
- better presentation of (e-) prescribing information at point-of-care?

Conclusions

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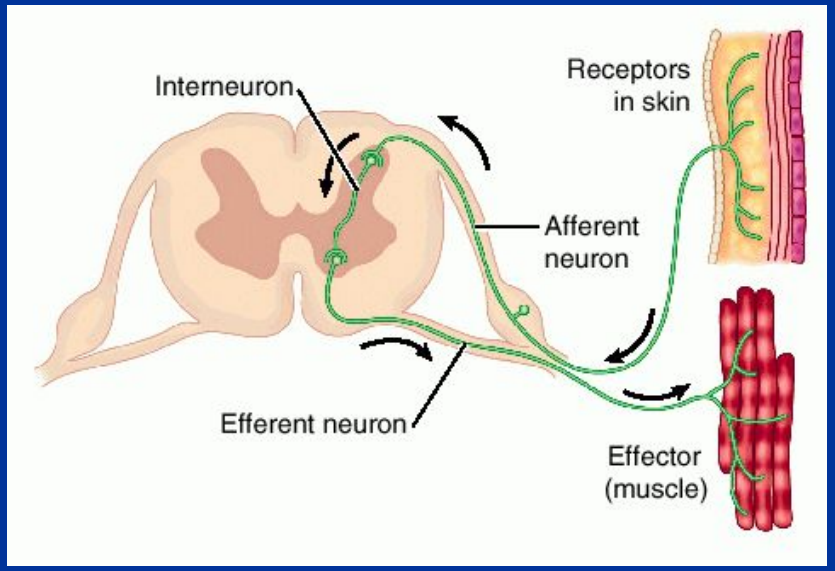
Future challenges – we will need to:

- fully integrate information based on different types of data and signals
- reach out to patients to understand their tolerance for risks and uncertainty
- engage with patients and health care providers to seek ways to further optimise utilisation of drugs in the marketplace



THANK YOU!

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