EUROPEAN PARLIAMENT

DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A
ECONOMIC AND SCIENTIFIC POLICY

Economic and Monetary Affairs

Employment and Social Affairs

Environment, Public Health and Food Safety

Industry, Research and Energy

Internal Market and Consumer Protection

Workshop on Effectiveness of Medicines and Therapies

MEETING DOCUMENT

EN

2013

Workshop on Effectiveness of Medicines and Therapies/Meeting Document

DIRECTORATE GENERAL FOR INTERNAL POLICIES
POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

WORKSHOP

Effectiveness of Medicines and Therapies

Brussels, 18 September 2013

MEETING DOCUMENT

ЕВРОПЕЙСКИ ПАРЛАМЕНТ PARLAMENTO EUROPEO EVROPSKÝ PARLAMENT EUROPA-PARLAMENTET
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Organised by the Policy Department A-Economy & Science for the Committee on the Environment, Public Health and Food Safety (ENVI)

Workshop on Effectiveness of Medicines and Therapies

Wednesday, 18 September 2013 from 13.00 to 14.45
European Parliament, Room A1G2, Brussels

AGENDA

13.00 - 13.05
Welcome and opening by Co-chairs of the Health Working Group, Alojz PETERLE and Glenis WILLMOTT, MEPs

13.05 - 13.10
Presentation of EC document "Investing in Health" (2013)
Mr Tapani PIHA, Head of Unit, e-Health and Health Technology Assessment, DG SANCO, European Commission.

Part 1
Efficacy and safety of new drugs and new therapies

13.10 - 13.20
Efficacy and/or effectiveness (confirmed)
Dr Francesco PIGNATTI, Head of Oncology, Haematology and Diagnostics at European Medicines Agency (EMA)

13.20 - 13.30
The need for comparative efficacy (confirmed)
Dr Jonathan CYLUS. Technical officer from European Observatory on Health Systems and Policies, London (UK)

13.30 – 13.40
The position and role of complementary and alternative medicines
Prof Dr Erik Baars. MD, MSc Epidemiology, University of Applied Sciences, Leiden, (NL)

13.40 - 13.55
Q&A

Part 2
Access to effective medicines and therapies through relative effectiveness policies

13.55 - 14.05
Relative effectiveness assessment systems: Assessing the effectiveness of medicines in comparison with other treatment options (confirmed)
Dr. Marcus MÜLLNER. Head of the Austrian Medicines and Medical Devices Agency (AGES PharmMed), Vienna (AT)

14.05 - 14.15
Useful, superfluous, unnecessary and dangerous drugs (confirmed)
Ms Lidija Gajski (MD), Croatian Association for Patients' Rights, Zagreb, (HR).

14.15 - 14.40
Open Discussion

14.40 - 14.45
Conclusions

14.45 Closing

SHORT BIOGRAPHIES OF EXPERTS

Mr Tapani Piha

Tapani Piha works as Head of Unit in the European Commission since 2004. First he managed the Health Law and International Unit, then the Human Resources Unit from 2009, and moved to the eHealth & Health Technology Assessment Unit in September 2012. The Unit works on expert advice for EU health systems, on health research and nano policies, Health Technology Assessment, eHealth and data protection issues.

A physician and specialist in community medicine and public health by training, he started his career in epidemiological and intervention research on health behaviours and cardiovascular disease. He held positions at the Finnish Ministry of Health working on health promotion and tobacco control. He coordinated Finland's EU policies in health in 1995-2001, based in first Helsinki and later in Brussels.

He joined the WHO Regional Office for Europe, in Copenhagen, for 5 years in 1989-1994 and was responsible for the Action Plan for a Tobacco-free Europe.

He is particularly interested in European integration as a unique process; the impact and effectiveness of health and other interventions; health and economy. His interest in information and communication technologies started in the 1970s.

Dr Jonathan Cylus

Jonathan Cylus is a research fellow at the European Observatory on Health Systems and Policies, based at the London School of Economics & Political Science. His work has been published in many scientific journals, including the Lancet, Health Affairs, BMJ, Health Services Research, Health Policy, and the European Journal of Public Health. Jonathan's primary research interests include comparative health policy, health system performance, and the effects of financial crises on health and health systems. Prior to joining the Observatory, Jonathan was an economist at the Centers for Medicare and Medicaid Services (CMS) in the United States where he was responsible for economic modelling of the US health care system. He has also acted previously as a consultant to a number of non-governmental organisations and international agencies. Jonathan holds degrees from the Johns Hopkins University and the London School of Economics & Political Science.

Prof Dr Erik Baars

Dr Erik Baars is currently Professor of Anthroposophic Healthcare at the University of Applied Sciences, Leiden, The Netherlands.

Since 2012 he has been scientific co-director of the European Scientific Cooperative on Anthroposophic Medicinal Products (ESCAMP). His particular research interest includes epidemiological and clinical studies, case-studies, health promotion, holism-reductionism, anthroposophic medicine, integrative medicine, concept development and methodology development for research and clinical practice.

For more than fifteen years he worked as an anthroposophic physician at the Zeylmans van Emmichoven Clinic and the Bernard Lievegoed Clinic in Bilthoven, The Netherlands. He is Master of Science in epidemiology and he has a PhD in curative health promotion.

Professor Dr Baars has published around 180 publications and is an editorial board member of the journals Healthcare and Medicines. Together with Professor Dr Peter Kooreman he received the 'Excellence in Integrative Medicine Research Award' (category 'clinical research') provided by the European Society of Integrative Medicine for the article 'Patients whose GP knows complementary medicine tend to have lower costs and live longer' in the European Journal of Health Economics (Kooreman & Baars, 2012).

Dr Marcus Müllner

Dr Marcus Müllner is Head of the Austrian Medicines and Medical Devices Agency since 2005. His appointment followed a year spent as a National Expert on secondment at the European Medicines Agency.

Dr Müllner followed a training course as a specialist in internal medicine (sub-speciality in intensive care) at the Austrian Medical Association in 2003, after which he worked as a senior physician at the Department of Emergency Medicine at the General Hospital in Vienna. Between 2003 and 2004 Dr Müllner was a member of the Ethics Committee of the Hospital Association for Biometrics as well as a member of the Ethics Committee of the Medical University of Vienna in charge of emergency medicine.

He completed postgraduate training as a Master of Science in Epidemiology at the University College of London / London School of Hygiene & Tropical Medicine and headed for a year the postgraduate course "Clinical Investigator" at the Medical University of Vienna

In addition Dr Müllner was associate editor at the British Medical Journal and Statistical Editor for the Cochrane Collaboration. He is currently Associate Professor of Internal Medicine at the University of Vienna.

Dr Lidija Gajski

Dr Lidija Gajski currently works at the Health Care Centre in Zagreb. She has been working as a clinician for 27 years after she finished Zagreb University School of Medicine and specialised in internal medicine.

Her area of interest and activity is bioethics. Dr Gajski is a Board member and a Secretary of the Croatian Bioethics Society. She is also a member and an advisor of the Croatian Association for Patients' Rights.

Dr Gajski is the author of the book *Lijekovi ili prica o obmani* (Medicaments or a Matter of Deception) published in 2009 in Croatian. The book is a comprehensive critique of the modern medicine, notably its commercialization and the corrupt alliance of pharmaceutical industry, medical profession and politics. The book gained attention and positive feedback from the public. Since the publication of the book, Dr Gajski has made hundreds of appearances in the media, delivered numerous lectures, participated in public discussions and scientific and professional meetings within and outside Croatia. Dr Gajski is also a coauthor of the book Corruption in Croatian Healthcare (2010).

PRESENTATIONS

Dr Jonathan Cylus

The red pill or the blue pill?

The need for comparative efficacy

Jonathan Cylus
18 September 2013

LSE Health

European Observatory on Health Systems and Policies

"What is the drug of choice for condition X?"

- High cholesterol?
  - Simvastatin, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, or rosuvastatin?
- Rheumatoid arthritis?
  - Abatacept, Adalimumab, Anakinra, Certolizumab, Etanercept, Golimumab, Infliximab, Rituximab, Tocilizumab
- Depression?
  - SSRIs, MAOIs, TCAs and more!

Ely JW, Osheroff JA, Gorman PN, Ebell MH, Chambliss ML, Pifer EA, et al. A taxonomy of generic clinical questions: classification study. BMJ 2000;321(7258):429-32.

Oftentimes, we don't know how Drug A compares to Drug B

How to choose then?

- Comparative (relative) efficacy
  - Comparing how "good" an intervention is *relative to other existing interventions* under ideal conditions

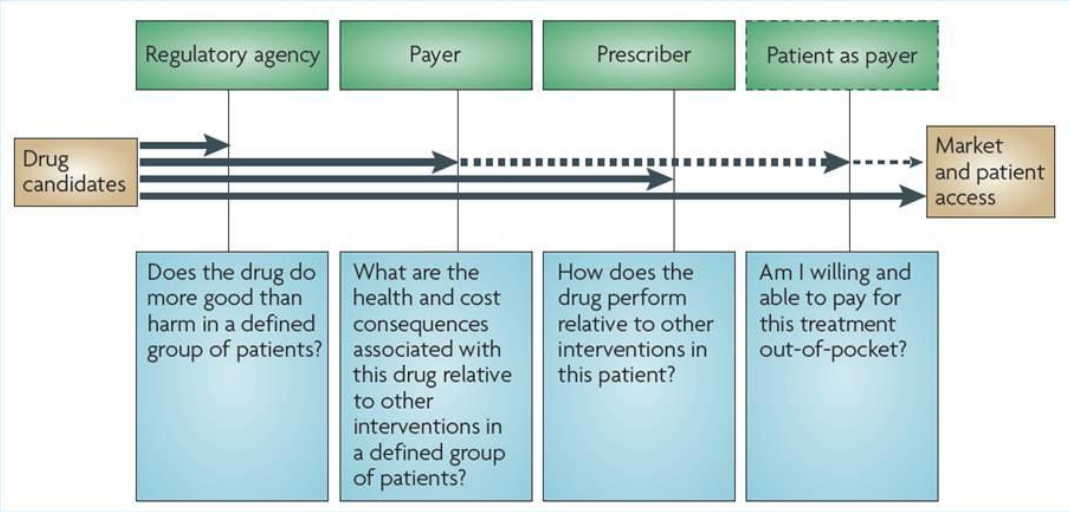
- Why not compare costs?
  - Costs differ by country, health system

Who needs comparative information?

- Manufacturers
- Regulators
- Payers
- Providers
- Patients

Every **downstream decision** needs comparative evidence

What are the objectives of each?



Eichler et al (2010), Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nature Reviews.

Who has this evidence **now**?

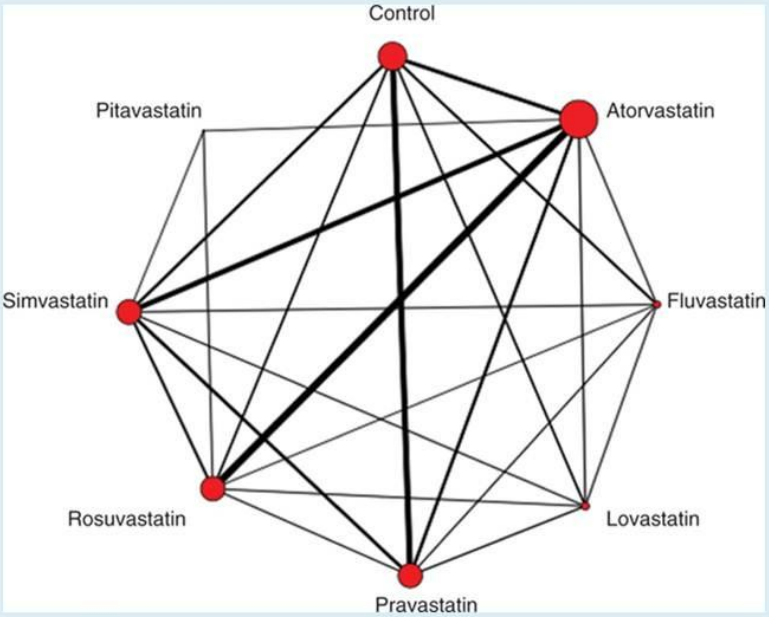
- **Manufacturers**
  - Not usually at the time of submitting for market approval
- **Regulators*, ****
  - Not always at time of market approval (not typically required)
- **Payers/HTA bodies**
  - Often generate this evidence themselves
- **Providers**
  - Sometimes but not systematically
- **Patients**
  - Sometimes but generally depend on providers

* van Luijn, et al (2007) Availability of comparative trials for the assessment of new medicines in the EU at the moment of market authorization, British Journal of Clinical Pharmacology
** Goldberg et al (2011) Availability of Comparative Efficacy Data at the Time of Drug Approval in the US. JAMA

How can we improve access to comparative information?

- Expensive and complicated for manufacturer to invest in trials to compare its product to all existing agents
- **Network meta analysis** is one option
  - Compare drug to all other comparators
  - Combines data from trials for various drugs
  - Placebo can be “common” comparator
  - Currently used by many HTA agencies

Network meta-analysis example



Naci H et al. Circ Cardiovasc Qual Outcomes 2013;6:390-399

Looking to the future: Making comparative evidence a formal part of **regulatory policy**

- Need for consistency
- Making sure trials are comparable*
- Overcoming concerns of manufacturers
- Making comparative evidence more visible to prescribers and patients
- Making phase 3 trial data publicly available would take some of the burden off of regulators**

* Heres et al (2006) Why olanzapine beats risperidone, risperidone beats quetiapine and quetiapine beats olanziapine: an exploratory analysis of head-to-head comparison studies of second-generation antipyschotics. AM J Psychiatry

**Eichler et al (2012) Open Clinical Trial Data for All? A view from regulators. PLOS Medicine.

Expected effects of greater availability of comparative evidence

1. Encouraging innovation*

- Target classes with few drugs
- Research shows steady increase in first-in-class drugs** even as comparative efficacy becomes more common

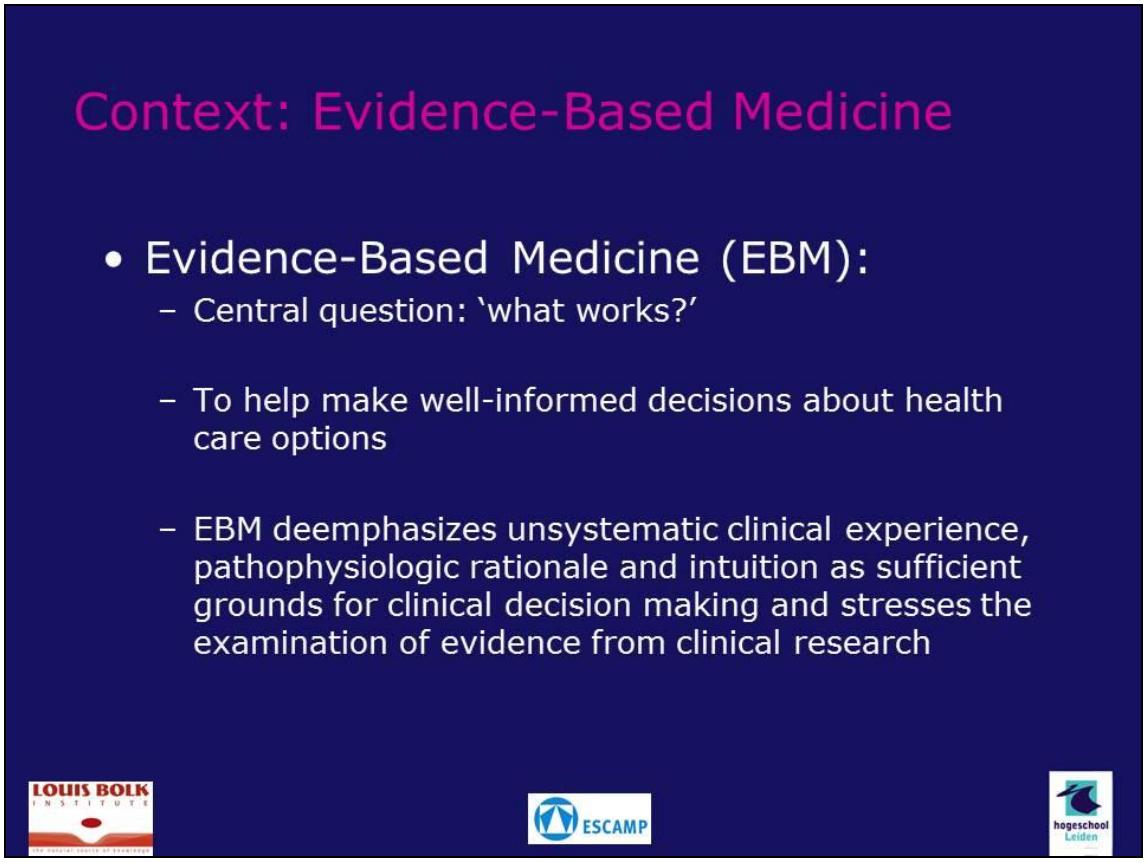
2. Faster approvals by payers

3. More patient-centred treatment

* Naci, Cylus, et al (2012) Raising the bar for market authorisation of new drugs. BMJ
** Lanthier et al (2013) An Improved Approach to Measuring Drug Innovation Finds Steady Rates of First-in-class Pharmaceuticals, 1987-2011

Thank you for your attention!

Presentation by Prof. Dr. Erik W. Baars


Context: Evidence-Based Medicine
• Evidence-Based Medicine (EBM):
– Central question: 'what works?'
– To help make well-informed decisions about health care options
– EBM deemphasizes unsystematic clinical experience, pathophysiologic rationale and intuition as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research
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Context: Evidence-Based Medicine
• Clinical research evolved into EBM, its goal being to integrate best (external) scientific evidence, individual clinical expertise, and patient perspective.
• EBM developed into a top-down approach:
– increasing regulation of the medical profession
– increasing regulation regarding the availability and reimbursement of therapies
– marginalizing the role of clinical expertise and patient perspective
• Basic assumption of EBM health policy:
– the "best evidence" reflects the "best therapy available"
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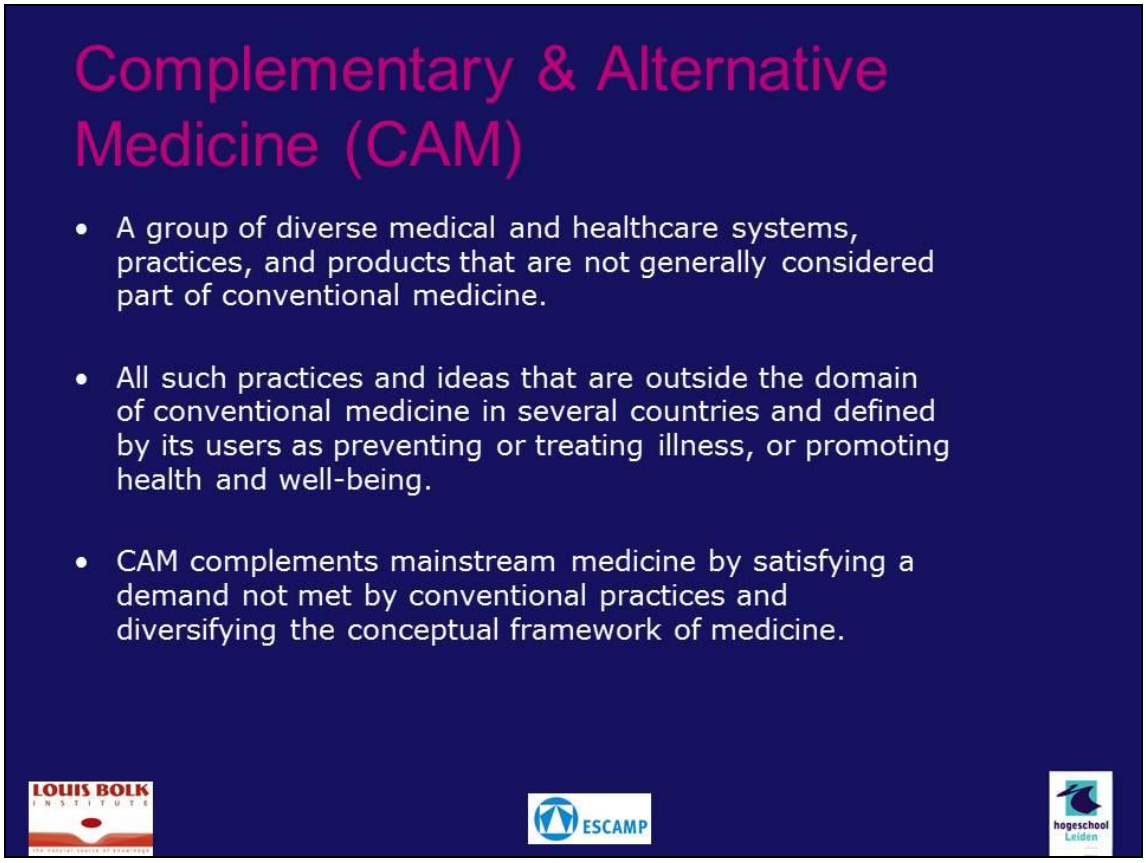
Complementary & Alternative Medicine (CAM)
• A group of diverse medical and healthcare systems, practices, and products that are not generally considered part of conventional medicine.
• All such practices and ideas that are outside the domain of conventional medicine in several countries and defined by its users as preventing or treating illness, or promoting health and well-being.
• CAM complements mainstream medicine by satisfying a demand not met by conventional practices and diversifying the conceptual framework of medicine.
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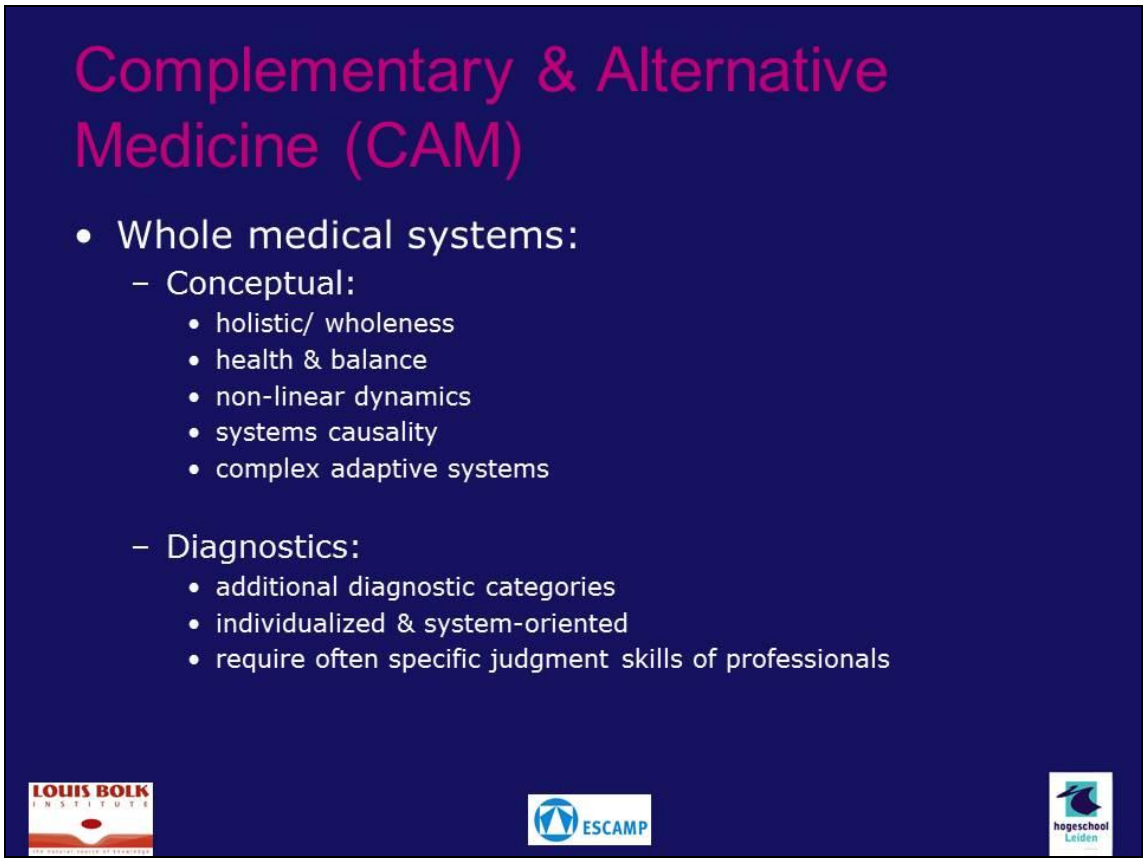
Complementary & Alternative Medicine (CAM)
• Whole medical systems:
– Conceptual:
• holistic/ wholeness
• health & balance
• non-linear dynamics
• systems causality
• complex adaptive systems
– Diagnostics:
• additional diagnostic categories
• individualized & system-oriented
• require often specific judgment skills of professionals
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Complementary & Alternative Medicine (CAM)

- Whole medical systems:
  - Treatment:
    - The focus is on the individual sick patient in his or her whole complexity, including physical, mental, spiritual and social factors. These are interconnected and need to be addressed in total and on multiple levels.
    - The repertoire of CAM treatment is complex, and its application highly individualized. CAM treatments and counseling are provided as integrative systems with interacting components. Accordingly, the effect of complex approaches often are larger than the sum of the components' effects.
    - Therapies aim to support and stimulate autoprotective and (auto) salutogenetic potentials, mostly with the active cooperation of the patient or of his/her organism.

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CON and CAM: traditional differences

- CON:
  - *Worldview*:
    - biomedical/ humanistic model
  - *Health*:
    - default situation
    - machine
  - *Disease*:
    - breakdown of the machine
  - *Treatment*:
    - group oriented guidelines/ protocols
    - fighting disease
    - requires external resources
- CAM:
  - *Worldview*:
    - holistic/ spiritual model
  - *Health*:
    - result of organism activity
    - wholeness/ balance
  - *Disease*:
    - expression of system imbalance
  - *Treatment*:
    - complex individualized interventions
    - health promotion
    - requires internal resources

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CON and CAM medicines: different pathways in development

New isolated chemicals Conventional drug therapy	Health systems Complementary medicine
Pre-clinical studies (biological mechanism, in vitro, in vivo; pharmacokinetics, pharmacodynamics)	Clinical practice
↓	↓
Clinical studies (Phase I → Phase III)	Clinical studies
↓	↓
Clinical practice	Pre-clinical studies

Kienle et al. Explore (NY) 2011
Adapted from: Fønnebø et al. BMC Med Res Methodol 2007

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CON and CAM: integration in Integrative Medicine

- Integrative Medicine (IM):
  - The coaching role of the doctor and the co-producer role of the patient
  - The active role of the patient in prevention (lifestyle), well-being, and therapy and healing processes
  - The use of evidence-based safe and effective conventional and complementary therapies
  - The use of healing environments
- Many IM pillars are increasingly part of CON

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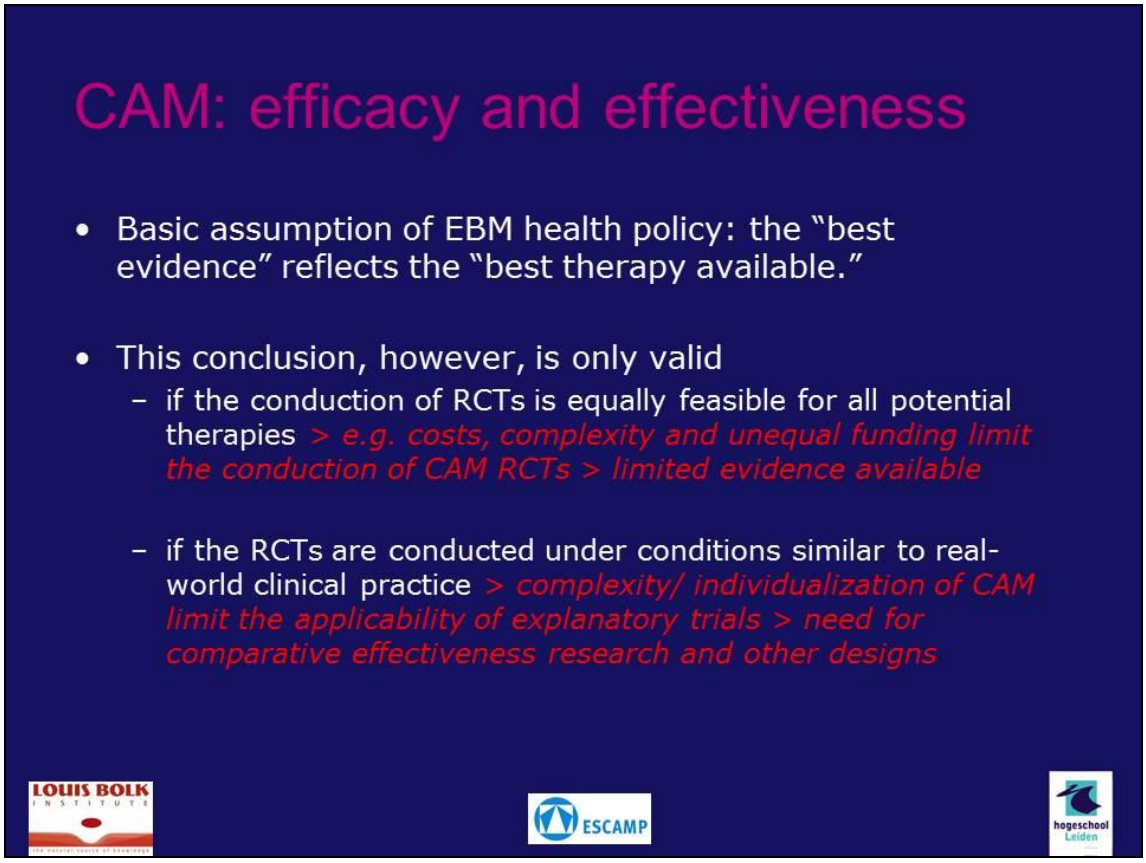
CAM: efficacy and effectiveness
• Basic assumption of EBM health policy: the "best evidence" reflects the "best therapy available."
• This conclusion, however, is only valid
– if the conduction of RCTs is equally feasible for all potential therapies > e.g. costs, complexity and unequal funding limit the conduction of CAM RCTs > limited evidence available
– if the RCTs are conducted under conditions similar to real-world clinical practice > complexity/ individualization of CAM limit the applicability of explanatory trials > need for comparative effectiveness research and other designs
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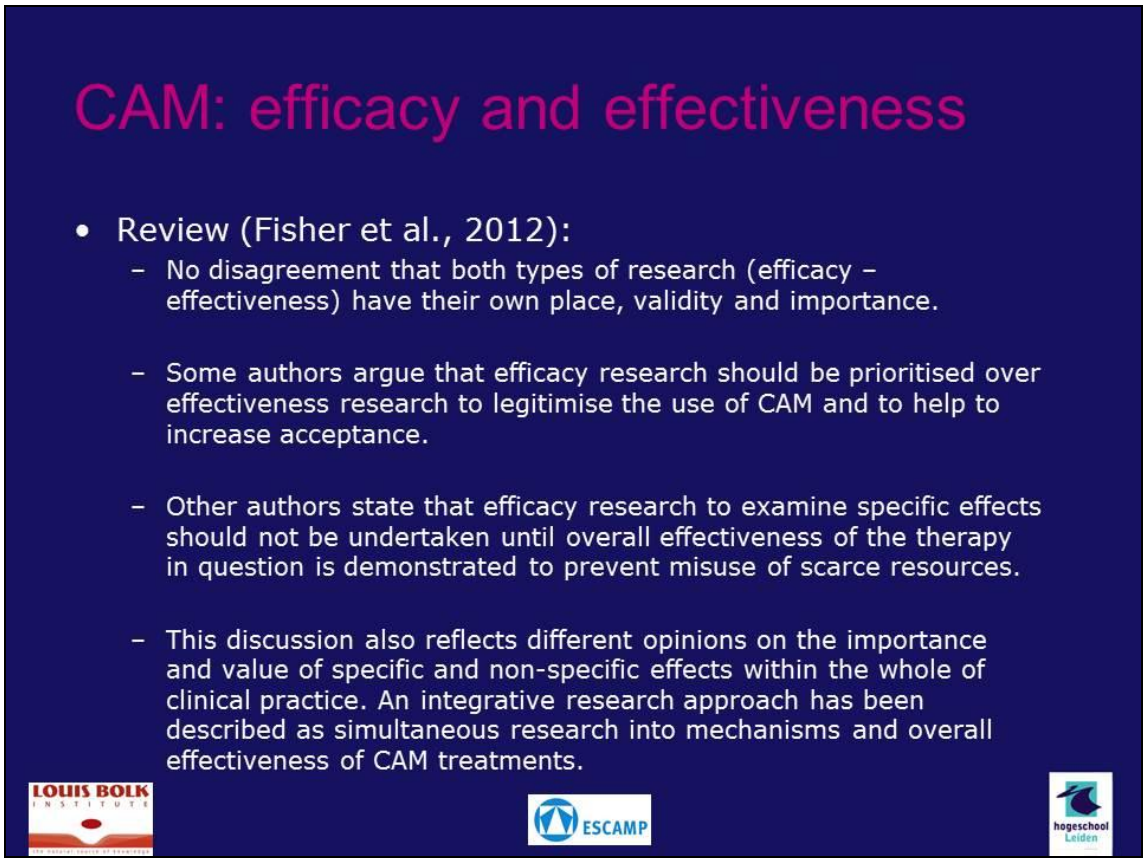
CAM: efficacy and effectiveness
• Review (Fisher et al., 2012):
– No disagreement that both types of research (efficacy – effectiveness) have their own place, validity and importance.
– Some authors argue that efficacy research should be prioritised over effectiveness research to legitimise the use of CAM and to help to increase acceptance.
– Other authors state that efficacy research to examine specific effects should not be undertaken until overall effectiveness of the therapy in question is demonstrated to prevent misuse of scarce resources.
– This discussion also reflects different opinions on the importance and value of specific and non-specific effects within the whole of clinical practice. An integrative research approach has been described as simultaneous research into mechanisms and overall effectiveness of CAM treatments.
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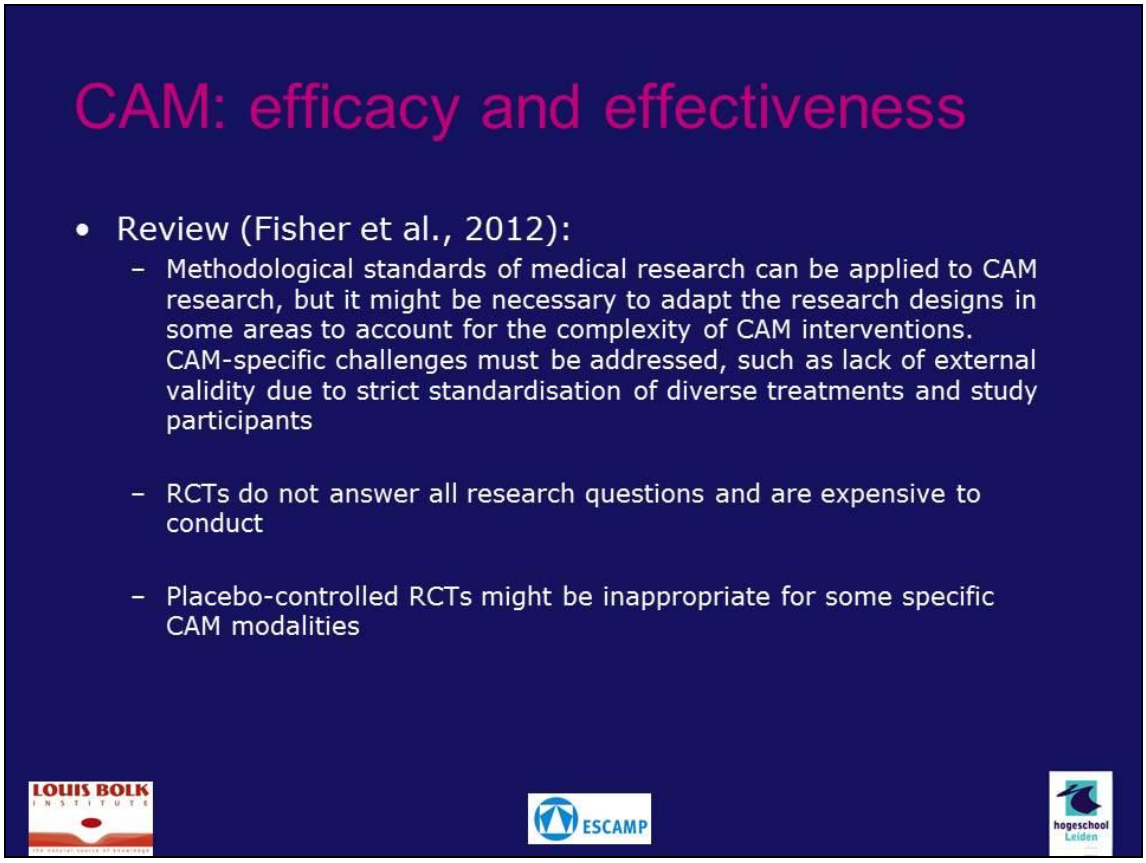
CAM: efficacy and effectiveness
• Review (Fisher et al., 2012):
– Methodological standards of medical research can be applied to CAM research, but it might be necessary to adapt the research designs in some areas to account for the complexity of CAM interventions. CAM-specific challenges must be addressed, such as lack of external validity due to strict standardisation of diverse treatments and study participants
– RCTs do not answer all research questions and are expensive to conduct
– Placebo-controlled RCTs might be inappropriate for some specific CAM modalities
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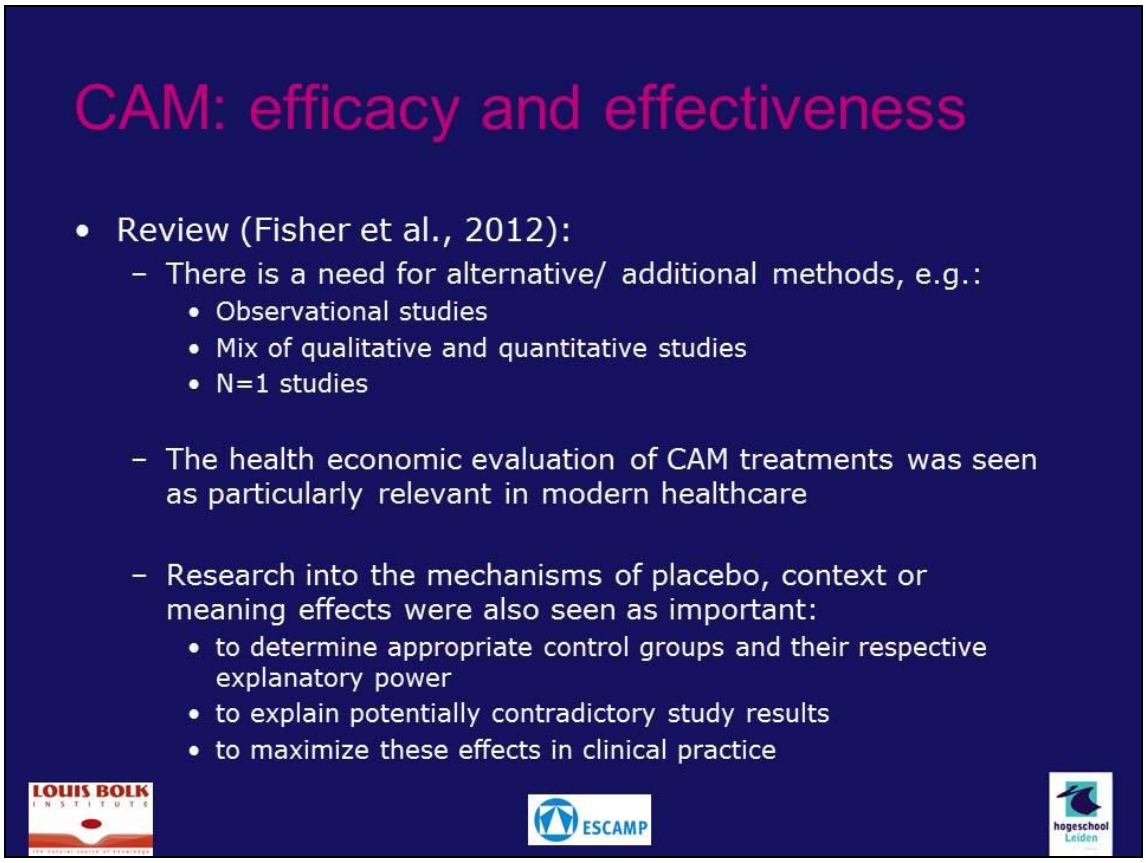
CAM: efficacy and effectiveness
• Review (Fisher et al., 2012):
– There is a need for alternative/ additional methods, e.g.:
• Observational studies
• Mix of qualitative and quantitative studies
• N=1 studies
– The health economic evaluation of CAM treatments was seen as particularly relevant in modern healthcare
– Research into the mechanisms of placebo, context or meaning effects were also seen as important:
• to determine appropriate control groups and their respective explanatory power
• to explain potentially contradictory study results
• to maximize these effects in clinical practice
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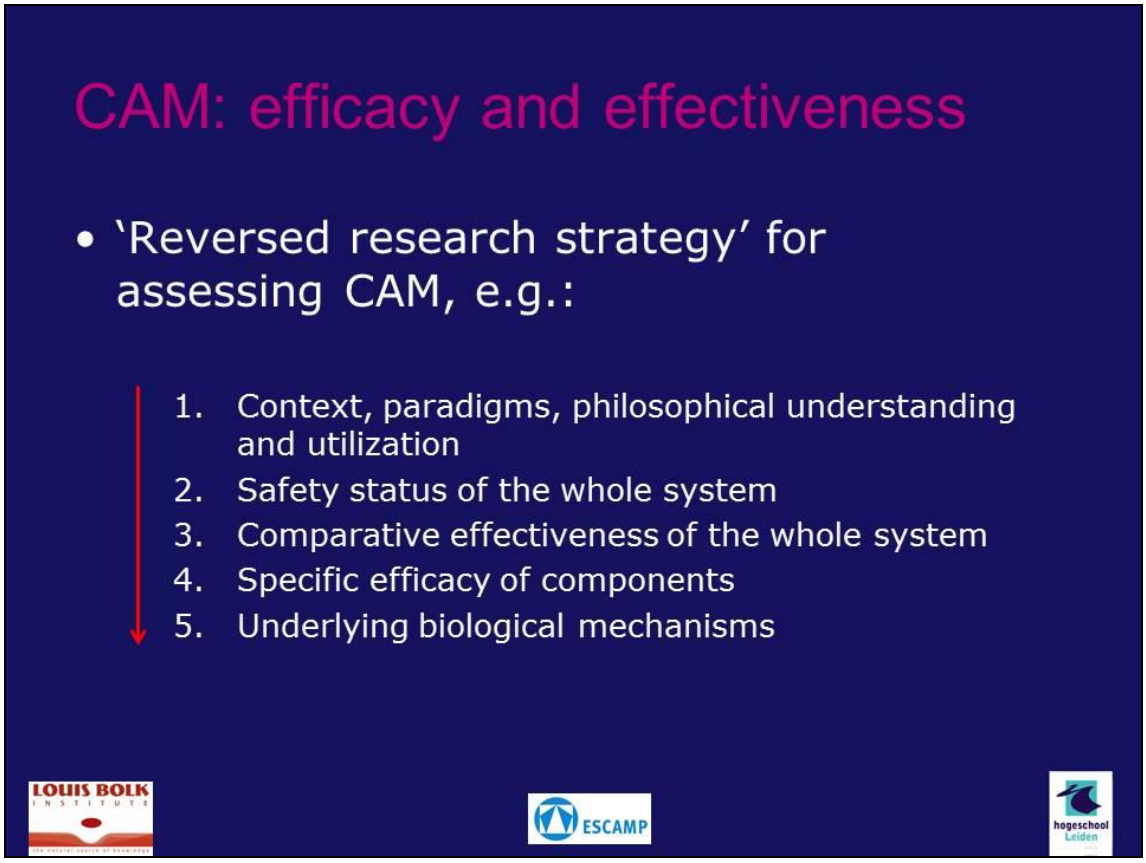
CAM: efficacy and effectiveness
• 'Reversed research strategy' for assessing CAM, e.g.:
1. Context, paradigms, philosophical understanding and utilization
2. Safety status of the whole system
3. Comparative effectiveness of the whole system
4. Specific efficacy of components
5. Underlying biological mechanisms
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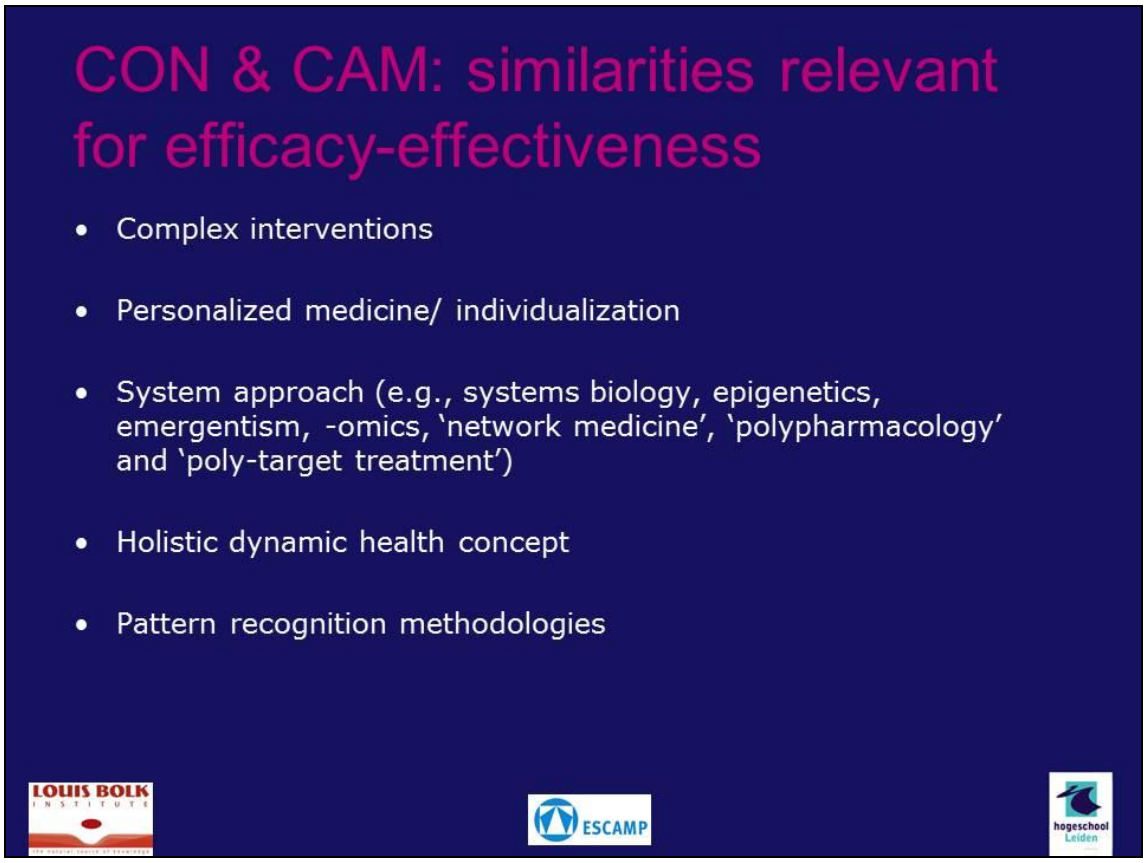
CON & CAM: similarities relevant for efficacy-effectiveness
• Complex interventions
• Personalized medicine/ individualization
• System approach (e.g., systems biology, epigenetics, emergentism, -omics, 'network medicine', 'polypharmacology' and 'poly-target treatment')
• Holistic dynamic health concept
• Pattern recognition methodologies
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CON & CAM: similarities relevant for efficacy-effectiveness

- RCTs are not applicable everywhere > shift towards more pragmatic trials
- Limitations in conducting clinical studies due to costs and complexity
- In many complex medical fields (e.g. paediatrics), evidence-based practice is only marginal and often critically questioned
- The use and role of professional judgment in clinical practice (e.g., X-rays)
- The increasing role of patient preferences and patient autonomy

Conclusions

- Both for CON and CAM:
  - The integration of the best of both worlds of the fighting disease and health promotion approaches (IM) is developing.
  - There are limitations in the conduction of clinical studies due to limited financial resources > lack of evidence.
  - There is a need for pluralism in study designs.

Conclusions

- Both for CON and CAM:
  - The systems approach, complexity and individualization in clinical practice require more (renewed) attention towards professional clinical decision making in clinical practice and clinical studies.
  - The increasing role of patients requires more attention towards patient preferences in clinical practice and clinical studies.
  - Several described issues undermine the central assumption of EBM that the "best evidence" reflects the "best therapy available."

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Thank you for your attention!

- **More information:**
  - Email: baars.e@hsleiden.nl
  - Websites: www.hsleiden.nl/lectoraten/professorship-anthroposophic-healthcare
    www.louisbolk.org/nl/home
    www.escamp.org

- **Important literature:**

- HF Fischer, F Junne, C Witt, et al. (2012). Key Issues in Clinical and Epidemiological Research in Complementary and Alternative Medicine – a Systematic Literature Review. Forsch Komplementmed 19(2):51–60 (DOI:10.1159/000343126)

- V Fønnebo, S Grimsgaard, H Walach, et al. (2007). Researching complementary and alternative treatments – the gatekeepers are not at home. BMC Med Res Methodol 2007, 7:7.

- PM Herman, BL Poindexter, CM Witt, DM Eisenberg (2012). Are complementary therapies and integrative care cost-effective? A systematic review of economic evaluations. BMJ Open;2:5 e001046 doi:10.1136/bmjopen-2012-001046

- GS Kienle, H-U Albonico, L Fischer, et al. (2011). Complementary therapy systems and their integrative evaluation. Explore: The Journal of Science and Healing, 7(3):175-87.

- P Kooreman, EW Baars (2012). Patients whose GP knows complementary medicine tend to have lower costs and live longer. The European Journal of Health Economics, 13(6):769-776.

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Presentation by Dr. Marcus Müllner

Relative effectiveness assessment systems:
Assessing the effectiveness of medicines in comparison with other treatment options

Marcus Müllner

18. September 2013

www.ages.at

Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH

What is it and why is it important?

- It is simply comparing, if a new therapeutic agent adds to what is already available.
- However ...

http://en.wikipedia.org/wiki/Apples_and_oranges

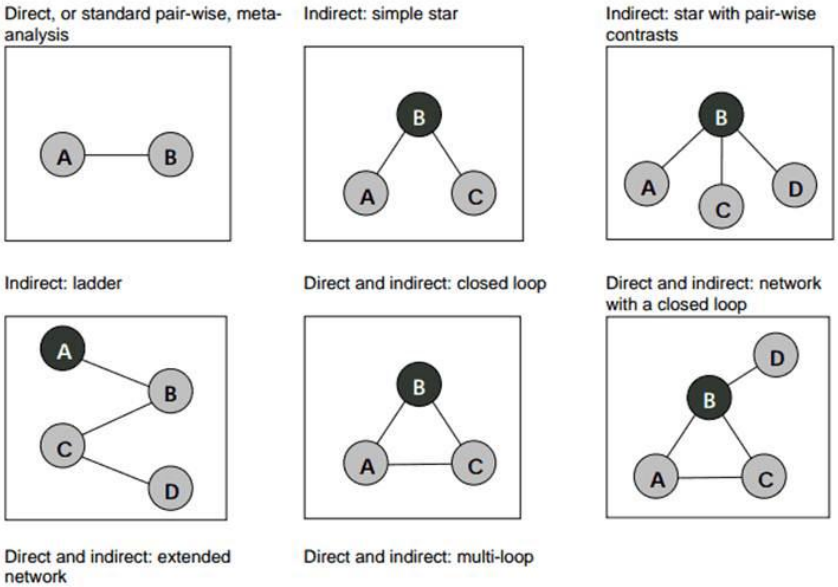
Is available information fit for purpose?

The base of the iceberg … what kind of comparisons are possible?

- Direct
- Indirect
- Mix of both

A few examples of possible comparisons…

Figure 1. Types of evidence network



http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf

An example of a **direct** comparison

- Lucentis (ranibizumab)

4.1 Therapeutic indications

Lucentis is indicated in adults for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1).
- the treatment of visual impairment due to diabetic macular oedema (DME) (see section 5.1).
- the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1).

- Head-to-head RCT: Ranibizumab (Lucentis) for the treatment of AMD as compared to standard care (and placebo) or verteporfin PTD - decrease of visual impairment in about 5% vs 36% (see EPAR).
- This results in a NNT of about 3.

An example of an **indirect** comparison

BMJ

BMJ 2012;345:e5182 doi: 10.1136/bmj.e5182 (Published 13 August 2012) Page 1 of 16

RESEARCH

The relative clinical effectiveness of ranibizumab and bevacizumab in diabetic macular oedema: an indirect comparison in a systematic review

An example of an indirect comparison

- **Types of trials included…**

Study	No of included eyes	Intervention	Comparison	Outcome	Baseline CMT and BCVA	Baseline exposure to laser therapy
Michaelides 2010 (BOLT study),[20 21] UK	80 eyes with centre-involving CSMO and ≥1 prior laser	1.25mg IVB 6 weekly (No of injections, range 3–9)	Laser alone 4 monthly (min 1 and max 4)	Mean difference of BCVA at 12 months	BCVA=55.2 letter score CMT=494.65 µm	80 experienced, 150 naive
Soheilian 2009,[22–24] Iran	150 eyes with CSMO with no previous treatment	Group 1. 1.25 mg IVB (retreatment at 12 week intervals if indicated) + sham laser Group 2. 1.25 mg IVB and 2 mg IVT (retreatment at 12 week intervals if indicated) + sham laser	Laser + sham injection (retreatment at 12 weeks intervals if indicated)	Mean difference of BCVA at 6 months	BCVA=0.66 logMAR CMT=333.33 µm	
RESTORE 2011,[25] international multicentre	345 eyes with focal or diffuse DMO	Group 1. IVR 0.5 mg (monthly for 3 months then as required) + sham laser Group 2. IVR 0.5 mg (monthly for 3 months then as required) + laser (monthly as required)	Laser (monthly as required) + sham injection	Mean average change in BCVA from baseline to month 1through 12	BCVA=63.5 letter score CRT=418.5 µm	Not reported
Nguyen 2009 (READ-2 study),[26 27] US	126 eyes with DMO	Group 1. 0.5 mg IVR at 0, 1, 3 and 5 months, Group 2. 0.5 mg IVR at 0, 1, 3, and 5 months and laser at 0 and 3 months if required	Laser alone at 0 and 3 months if required	Change from baseline in BCVA at 6 months	BCVA=26.0 letters read EFT=229.65 µm	Not reported
DRCRN 2010,[28 29] US	854 eyes with DMO	Group 1. 0.5 mg IVR with retreatment as required + prompt laser Group 2. 0.5 mg IVR with retreatment as required + deferred laser Group 3. 4 mg IVT with retreatment as required + prompt laser	Group 4. Sham injection + prompt laser	Change in BCVA at 12 months	BCVA=65.7 letter score* CST=386.4 µm*	489 experienced, 365 naive

CMT=central macular thickness, BCVA=best corrected visual acuity, CSMO=clinically significant macular oedema, IVB=intravitreal bevacizumab, laser=laser therapy, IVT=intravitreal triamcinolone, logMAR=logarithm of minimum angle of resolution, DMO=diabetic macular oedema, IVR=intravitreal ranibizumab, CRT=central retinal thickness, EFT=excess foveal thickness, CST= central subfield thickness.

An example of an indirect comparison

Outcome estimates and their precision …

Table 6: Indirect comparisons of ranibizumab and bevacizumab for treatment of diabetic macular oedema: proportion with improvement of >2 lines on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale

Indirect comparison	Odds ratio (95% CI)*
Main analysis: bevacizumab *v* ranibizumab alone	0.95 (0.23 to 4.32)
Bevacizumab *v* ranibizumab + prompt laser	0.80 (0.19 to 3.11)
Bevacizumab *v* ranibizumab + deferred laser	0.61 (0.12 to 2.84)

CI=credible interval.

*Odds ratios >1 indicate a treatment effect in favour of ranibizumab.

- **Problem 1**

Conclusions Results suggest no difference in effectiveness between bevacizumab and ranibizumab, but the wide credible intervals cannot exclude the possibility that either drug might be superior. Sufficiently powered, direct head to head trials are needed.

An example of an indirect comparison

AGES

- **Problem 2**

What is Avastin used for?

Avastin is used to treat the following types of cancer in combination with other chemotherapy medicines (medicines to treat cancer):

- cancer of the colon or rectum (large intestine) that is metastatic (has spread to other parts of the body), in combination with chemotherapy that includes a 'fluoropyrimidine';
- metastatic breast cancer, in combination with paclitaxel or capecitabine;
- advanced, metastatic or recurrent non-small-cell lung cancer, in combination with chemotherapy that includes a 'platinum-based' medicine;
- advanced or metastatic kidney cancer, in combination with interferon alfa-2a;
- advanced epithelial cancer of the ovary, advanced cancer of the fallopian tube or the peritoneum (the membrane lining the abdomen), in combination with carboplatin and paclitaxel;
- first recurrence of epithelial cancer of the ovary, cancer of the fallopian tube, or the peritoneum, in combination with carboplatin and gemcitabine.

See the summary of product characteristics (also part of the EPAR) for more information.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000582/human_med_000663.jsp&mid=WC0b01ac058001d124

Is available information fit for purpose?

AGES

A few limitations of direct and indirect comparisons…

- DC only available for limited indications, usually efficacy (unless pragmatic, ie non GCP megatrials)
- IDC use data often not fit for purpose (trial quality, data-coding and missing values, publication bias and heterogeneity). More often than not "more research required"

Is available information fit for purpose?

AGES

The rest of the iceberg…

- Clinical endpoints;
- Composite endpoints;
- Surrogate endpoints;
- Safety;
- Health related quality of life;
- Choice of comparator;
- Internal validity;
- Applicability.

(see EUnetHTA WP 5 http://www.eunethta.eu/activities/JA-WP5/ja-wp5-relative-effectiveness-assessment-pharmaceuticals

The question is not so much how but when and who!

AGES

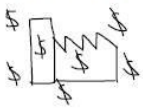
Who?

The key players…

Market authorisation

Reimbursement

Industry



Academia
&
Doctors

The question is not so much how but when and who!

AGES

When?

- Before (scientific advice) and at MA?
- At the reimbursement application?
- After MA (using eg Post Authorisation Efficacy Studies)?

Without curbing innovation and delaying access to innovative medicines?

We have the scientific tools …

AGES

… but what is the way forward to get the materials?

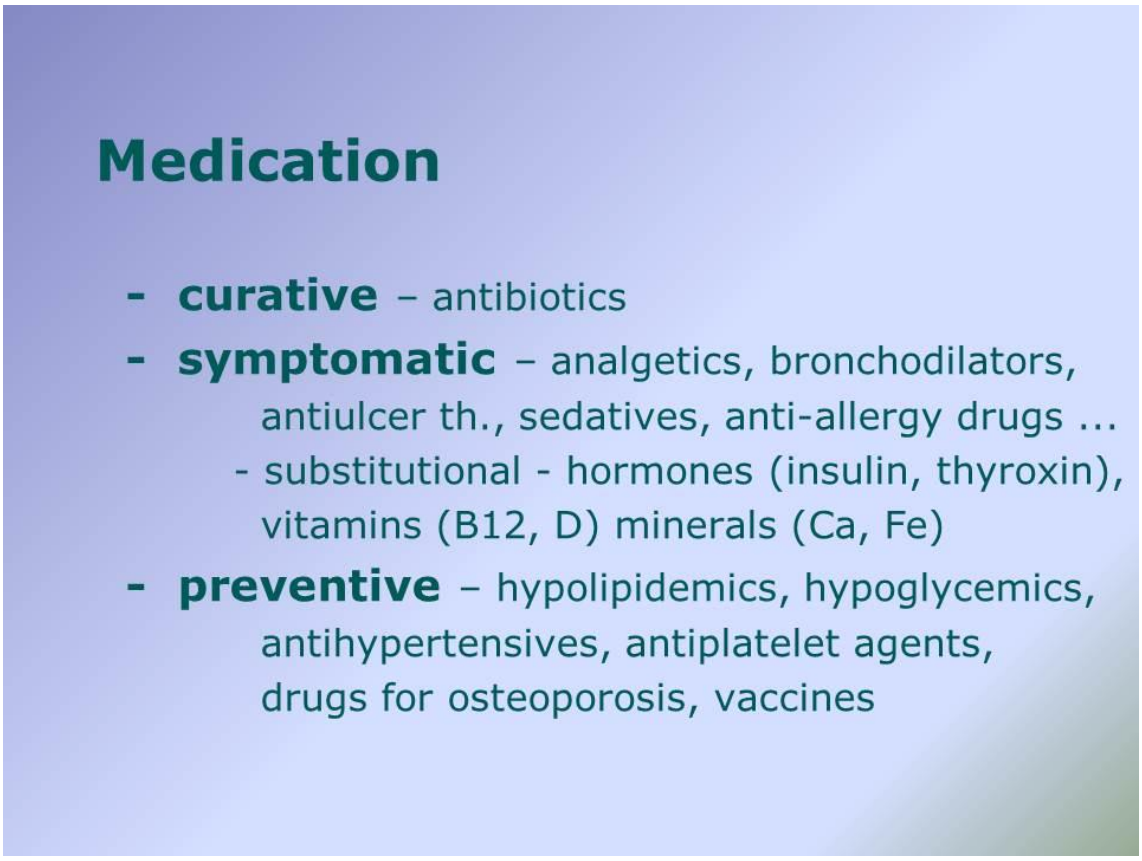
- Do we have a sufficient legal framework?
- Do we have a sufficient operational framework?
- Do we have a sufficient technical framework (ICT)?

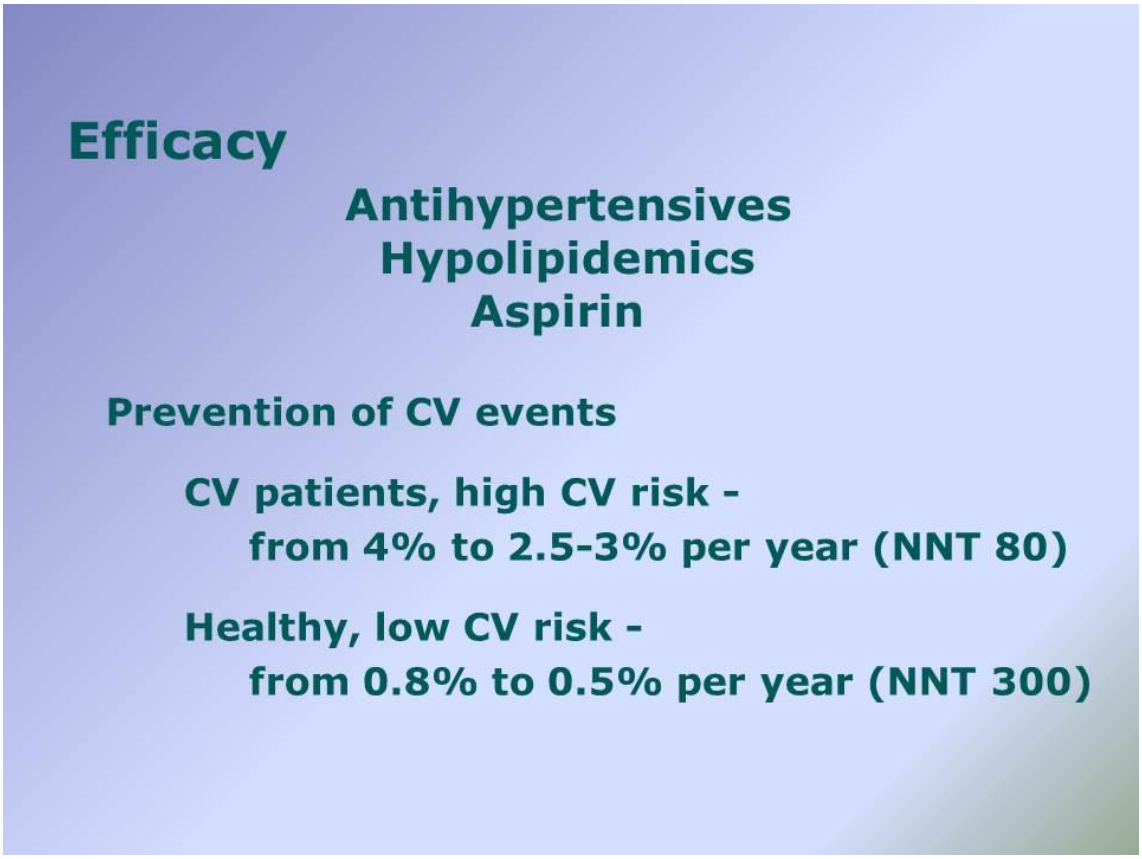
… *if not, EU heterogeneity incorporated in an inefficient way…*

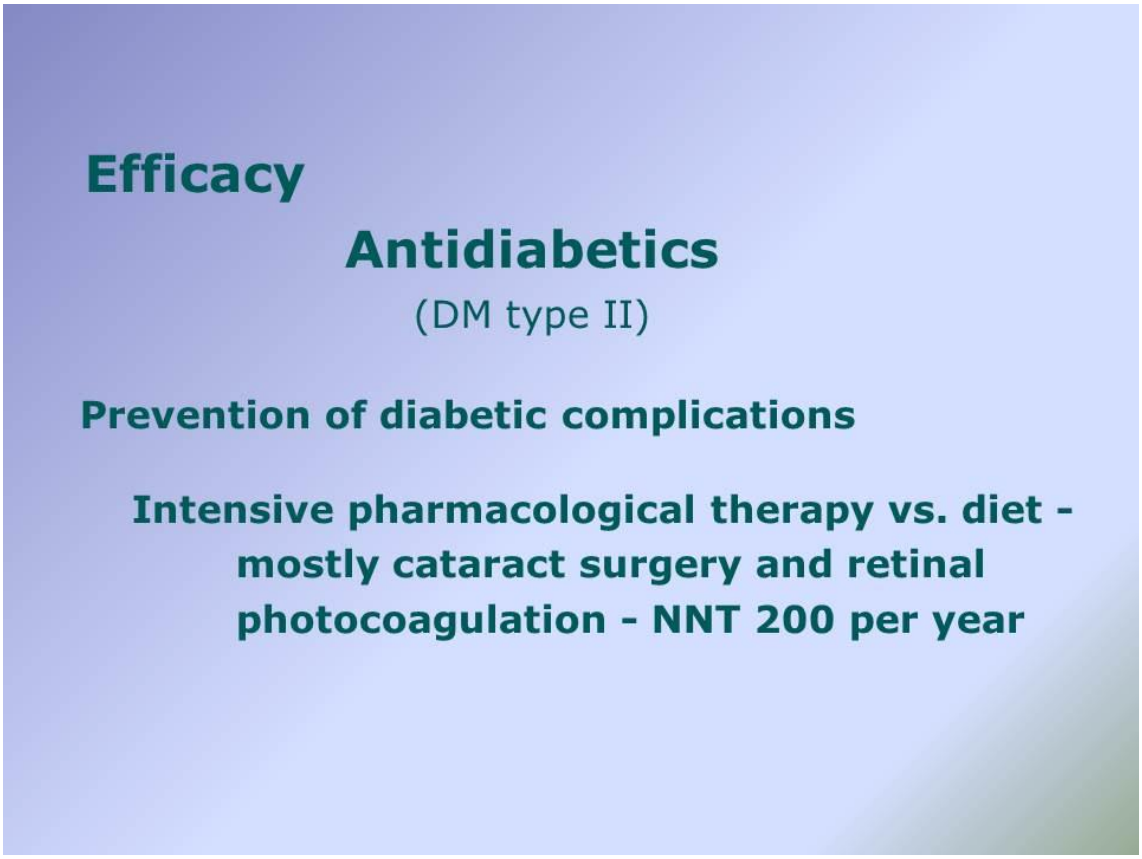
1 + 1 = 0,2

- Are there sufficient incentives for innovation AND REA?

Presentation by Dr Lidija Gajski




Efficacy
Antihypertensives
Hypolipidemics
Aspirin
Prevention of CV events
CV patients, high CV risk -
from 4% to 2.5-3% per year (NNT 80)
Healthy, low CV risk -
from 0.8% to 0.5% per year (NNT 300)


Efficacy
Antidiabetics
(DM type II)
Prevention of diabetic complications
Intensive pharmacological therapy vs. diet -
mostly cataract surgery and retinal
photocoagulation - NNT 200 per year

Efficacy

Drugs for osteoporosis – hip fracture – NNT 500 per year
HRT – symptomatic; no long-term benefit
Weight loss drugs – minimal effect
Antidepressants – modest efficiency in severe depression only
Chemotherapy – no effect in most common cancers
Antiviral drugs – very limited effects
Vaccines – unknown

Effectiveness < Efficacy

RCCT bias – sample selection, intention-to-treat, compliance, adverse effects, follow-up period, … funding –

– private financing 4-5 x more often favoring sponsor's product

(Bekelman, JAMA 2003; Lexchin, BMJ 2003; Als-Nielsen, JAMA 2003)

Pharmaceutical industry - 70% RCCT

(Bodenheimer, NEJM 2000)

Pharmaceutical industry

- **overestimating drug benefits**
- **broadening drug indications** (SSRI, statins, erythropoietin)
- **exaggerating disease severity and prevalence** (influenza, hepatitis, migraine)
- **expanding disease definition** (asthma, depression, ADHD, erectile dysfunction, hypertension)
- **creating new clinical entities** (hyperlipidemia, osteoporosis, menopause, Helicobacter pylori, social anxiety disorder)

Medicalization

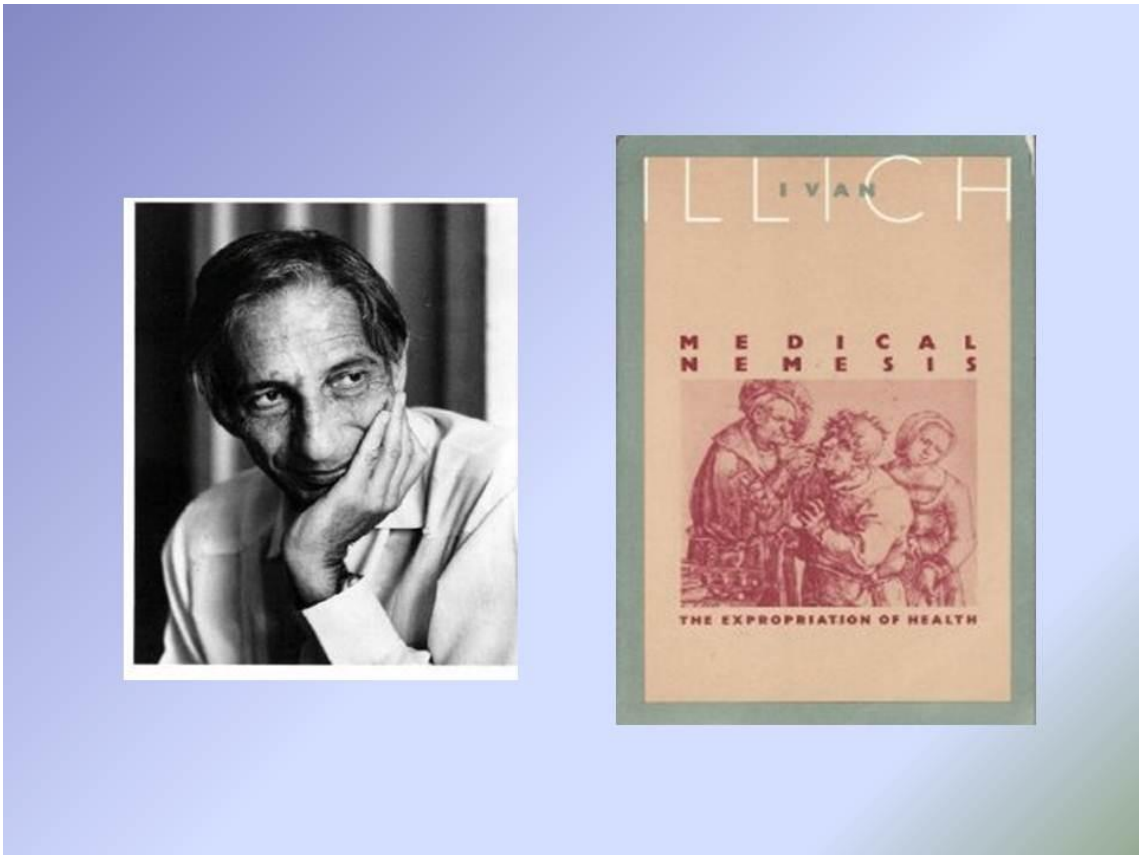
Transformation of normal life processes, physiological conditions and non-medical (social, interpersonal, intrapersonal) phenomena into medical problems in need of treatment by medical professionals

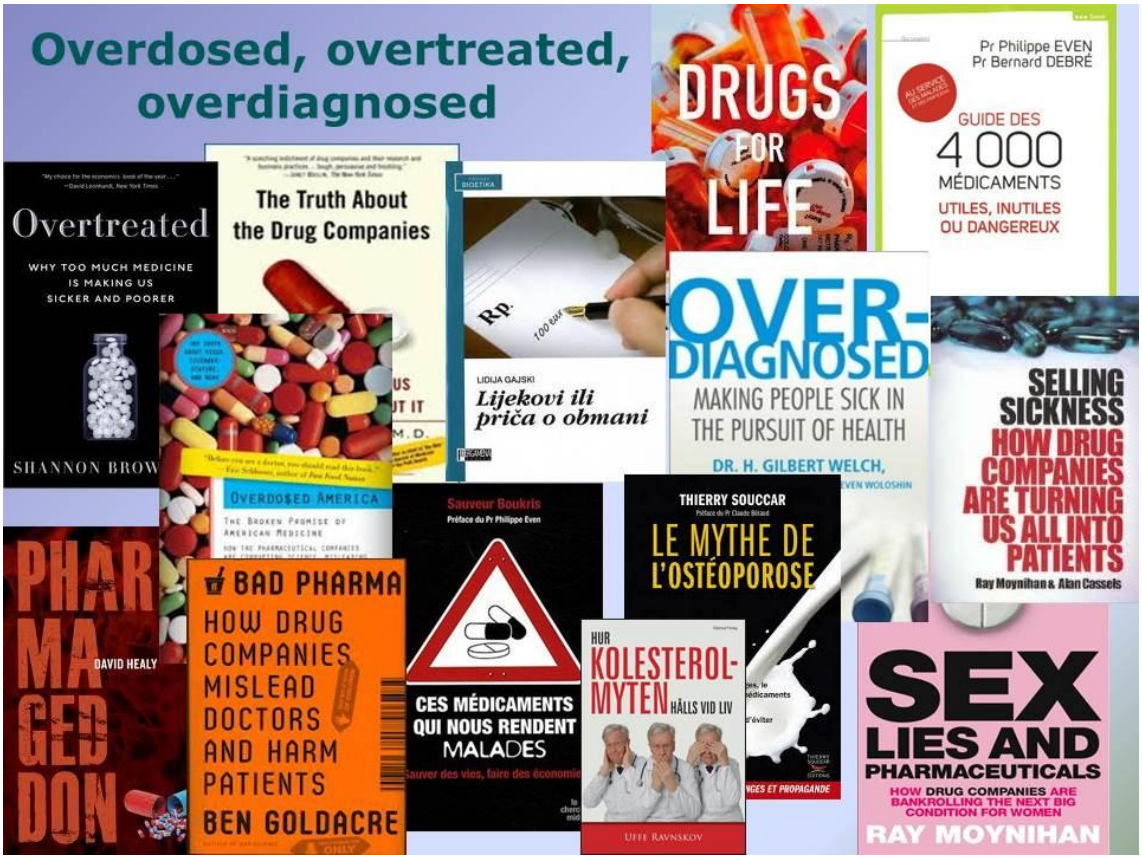
Prevention orientation

Medical paradigm shift – curative to preventive

Pharmacological prevention

⇒ **medical, economic, social, cultural harm**


ILLICH
MEDICAL NEMESIS
THE EXPROPRIATION OF HEALTH


Overdosed, overtreated, overdiagnosed
Overtreated
WHY TOO MUCH MEDICINE IS MAKING US SICKER AND POORER
SHANNON BROWN
The Truth About the Drug Companies
DRUGS FOR LIFE
Pr Philippe EVEN
Pr Bernard DEBRÉ
GUIDE DES 4 000 MÉDICAMENTS
UTILES, INUTILES OU DANGEREUX
LIDIJA GAJSKI
Lijekovi ili priča o obmani
OVER-DIAGNOSED
MAKING PEOPLE SICK IN THE PURSUIT OF HEALTH
DR. H. GILBERT WELCH,
SELLING SICKNESS
HOW DRUG COMPANIES ARE TURNING US ALL INTO PATIENTS
Ray Moynihan & Alan Cassels
OVERDOSED AMERICA
THE BROKEN PROMISE OF AMERICAN MEDICINE
PHARMAGEDDON
DAVID HEALY
BAD PHARMA
HOW DRUG COMPANIES MISLEAD DOCTORS AND HARM PATIENTS
BEN GOLDACRE
Sauveur Boukris
CES MÉDICAMENTS QUI NOUS RENDENT MALADES
THIERRY SOUCCAR
LE MYTHE DE L'OSTÉOPOROSE
HUR KOLESTEROL-MYTEN HÅLLS VID LIV
UFFE RAVNSKOV
SEX LIES AND PHARMACEUTICALS
HOW DRUG COMPANIES ARE BANKROLLING THE NEXT BIG CONDITION FOR WOMEN
RAY MOYNIHAN

Medication harm

Epidemiology

Outpatients (USA) - approx. 25% prescrip. drug users
- 18% (Gandhi, J Gen Intern Med 2000)

Hospitalized patients

USA - 1% fatal, 12% life-threatening,
30% serious (Bates, JAMA 1995)

- 6,7% (2,2 million) serious
- 0,32% (106 000) fatal (Lazarou, JAMA 1998)

UK (18 820 patients) - 6,5%
- 0,15% fatal (Pirmohamed, BMJ 2004)

- underestimated by official statistics and public perception

Medication harm

Cause

- **increasing use**
- **insufficient testing**
- **inadequate approval process**
- **poor post-marketing surveillance**

Marketing authorization

Clinical trial regulation insufficient to test drugs intended for chronic conditions, researchers say

Gaffney, RF 2013

Has the pharmaceutical industry skilfully managed to achieve an unhealthy influence over European drug regulatory agencies?

Abraham, BMJ 2002

The safety risks of innovation: the FDA's Expedited Drug Development Pathway

Moore, JAMA 2012

Drug-approval process may benefit from revisions

Psaty, JAMA 1999

Reductil banned in Europe

European Medicines Agency recommends withdrawal of benfluorex from the market in European Union

Avandia withdrawn from market

Conflict of interest

	Primary interest	Secondary interest
Pharma-ceutical industry	profit	social responsibility
Medical, political elite	social responsibility	profit

Conflict of interest

Resolution

- relationship with industry is beneficial and acceptable
  ⇨ regulation
- relationship with industry is harmful and unnecessary
  ⇨ elimination

EUROPEAN PARLIAMENT

DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT A
ECONOMIC AND SCIENTIFIC POLICY

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Policy departments are research units that provide specialised advice to committees, inter-parliamentary delegations and other parliamentary bodies.

Policy Areas

- Economic and Monetary Affairs
- Employment and Social Affairs
- Environment, Public Health and Food Safety
- Industry, Research and Energy
- Internal Market and Consumer Protection

Documents

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Workshop on Effectiveness of Medicines and Therapies/Meeting Document