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Effectiveness of Medicines and Therapies

WORKSHOP



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

WORKSHOP

Effectiveness of Medicines and Therapies

Brussels, 18 September 2013

PROCEEDINGS

Abstract ▼

This report summarises the presentations and discussions at the Workshop on “Effectiveness of Medicines and Therapies”, held at the European Parliament in Brussels, on Wednesday 18 September 2013. The aim of the workshop was to exchange views on the latest developments and main challenges healthcare systems have to address while assessing risks and benefits of new drugs and therapies. The workshop was hosted by MEP Mr Alojz PETERLE (EPP, SL), Co-chair of the Health Working Group within the ENVI Committee.

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LIST OF ABBREVIATIONS

CAM	Complementary & Alternative Medicines
CON	Conventional Medicines
DG SANCO	Directorate General for Health and Consumers
EBM	Evidence-based medicine
EC	European Commission
EMA	European Medicines Agency
ENVI	Committee on Environment, Public Health and Food Safety
EP	European Parliament
EU	European Union
HTA	Health Technology Assessment
IM	Integrative Medicine
MEP	Member of the European Parliament
PAESs	Post-authorisation efficacy studies
WHO	World Health Organization

EXECUTIVE SUMMARY

On 18 September 2013, the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament held a workshop on the “Effectiveness of Medicines and Therapies”. The workshop was hosted by Mr Alojz PETERLE (MEP), Co-chair of the Health Working Group within the ENVI Committee.

In his opening statement, Mr PETERLE highlighted that the development of a systematic approach to evaluate the risks and benefits of new drugs and therapies has become a central issue for EU health systems. Mr Peterle welcomed the speakers and the audience. While introducing the aims of the workshop, Mr PETERLE stated that effectiveness in healthcare is gaining more and more attention and welcomed the range of views the panellists were presenting. He added that “Efficiency, efficacy and effectiveness” are becoming the watchwords of the debate over healthcare systems but also that, “Patients are more concerned with how drug and treatments work and at what they cost, rather than about ideologies of healthcare.”

Mr Tapani PIHA, Head of Unit (eHealth and the Health Technology Assessment) at DG SANCO in the European Commission (EC) paved the meeting by giving a broad summary of the Commission’s role in this area. He outlined the European Commission proposals for supporting the reform of Member States’ healthcare systems, whilst maintaining core commitments to free access and high quality services. and its support for reforming Member States’ healthcare systems, whilst maintaining core commitments to free access and high quality services. He referred to the EC document “Investing in Health” under the Social Investment Package which has been accepted across the Member States and to the Directive on cross-border healthcare which offers tools for Member State cooperation. These tools include: an expert panel to advise on healthcare investments; an information sharing network to pool results from healthcare technology testing; and cooperation between eHealth networks. The Commission is also supporting effectiveness in healthcare systems through structural funds and programmes encouraging local and regional partnerships.

The workshop was structured in two parts. The first one was dedicated to the safety and efficacy of new drugs and therapies. The second one focused on the access to effective medicines and therapies through relative effectiveness policies.

In his presentation, Dr Francesco PIGNATTI, Head of Oncology, Haematology and Diagnostics at European Medicines Agency (EMA), focused on “Efficacy-Effectiveness: addressing the gap”. He highlighted that efficacy is defined as the ability of an intervention or drug to produce a desired effect in expert hands and under ideal circumstances. Effectiveness, on the other hand, is defined and measured under the usual circumstances of healthcare practice, i.e. post-trial and in real-world settings. Bearing these differences in mind, a drug or treatment that meets the efficacy criteria can be ineffective in real life. Dr PIGNATTI explained the role of the EMA in lessening this gap and in removing drugs from the market found to be ineffective in light of post-approval evidence. Despite the fact that EMA does not have relative comparative effectiveness test when assessing medicines, he considered that regulators should rely less on a ‘One-off’ licensing approach and should become more adaptive, with continuous assessments of medicines throughout their life-cycle. In this context, regulators can play a stronger role going forward in providing information to prescribers and patients on the use of their treatments, in making the most of registries of medicinal information and in focussing more on the results of pragmatic and effectiveness trials.

Dr Jonathan CYLUS, Technical officer from the European Observatory on Health Systems and Policies in London, gave a presentation on “The red pill or the blue pill: the need for comparative efficacy”. He argued that current health systems use insufficient comparative evidence to ensure effective treatment. He asserted that every downstream decision needs comparative evidence. Finding such evidence is however problematic and very expensive for individual firms. It is also not strictly necessary for a product approval. A solution could be to use ‘Network meta-analysis’- comparing a drug to a comparator and a placebo and then combining data from similar trials for various drugs. He argued that there is a strong role here for a European agency to lay down strong guidelines to enable such comparative trials. He concluded that the benefits of greater availability of comparative evidence would stimulate innovation and improve health outcomes; and that comparative evidence should also formally be made part of the regulatory process.

Prof Dr Erik BAARS, MD and MSc Epidemiology, University of Applied Sciences in Leiden, spoke on “The position and role of complementary and alternative medicines”. He outlined the increasing trend of using Complementary & Alternative Medicines (CAM) and compared and contrasted this with Conventional Medicines (CON). Measuring effectiveness has to date centred around ‘Evidence-based medicine’ (EBM), a basic assumption being that the ‘best evidence’ reflects the ‘best available therapy.’ Dr BAARS stated, however, that this is not always the case. He explained that CAM could complement and diversify our idea of medicine. It is holistic and non-linear, seeing patients and disease in a wider system of health and balance. Both conventional and complementary approaches are today being brought together in what Dr BAARS termed ‘Integrative Medicine (IM).’ In the IM context, both conventional and complementary medicine also face similarities in providing evidence for the effectiveness of complex and personal treatments, and for these treatments CAM approaches could be subject to similar efficacy and effectiveness tests as CON. This requires, however, additional methods and better funded and more ‘real world’ trials that are adapted to the complexity of CAM.

Ms Lidija GAJASKI, MD and member of the Croatian Association for Patients’ Rights, gave a presentation on “Useful, superfluous, unnecessary and dangerous drugs”. She began by outlining the three uses of medication: curative (e.g. antibiotics), preventive (e.g. vaccines) and symptomatic (sedatives, anti-allergy treatments.) Ms GAJASKI reviewed the efficacy of a number of drug categories and noted that their effectiveness and real-world impact was often less than the clinical efficacy found in laboratories. Ms GAJASKI also pointed out how the pharmaceutical industry has coloured our perception, overestimating for example some drug benefits and creating new clinical disease states (e.g. social anxiety disorder). She argued that we are often being overdosed, over-treated and over-diagnosed and are harming ourselves through the increasing use of medication, which are often insufficiently tested, go through inadequate approval processes and are subject to poor post-marketing surveillance. Ms GAJASKI considered that a conflict of interest between the pharmaceutical industry and regulatory agencies lay behind this. She said that better regulation was needed to improve the relationship between industry and regulatory agencies.

At the end of the workshop, Mr PETERLE expressed his gratitude to all speakers for the very interesting debate and fruitful discussion. He pointed out that, even though the sessions have been marked by some disagreements between experts and the audience, these have provided insight to the debate and will help find shared solutions.

1. LEGAL AND POLICY BACKGROUND

Ensuring that medicines are safe and effective is a central issue for EU health systems. By definition, a medicine or therapy is considered as effective if it does more good than harm when provided under the usual circumstances of health care practices. Before being authorised, all medicinal products are subject to clinical trials that test their quality, efficacy and safety. The EU regulates the ways in which clinical trials are carried out through the Clinical Trials Directive 2001/20/EC¹ which has been detailed further in the Good Clinical Practice Directive 2005/28/EC². The requirements under these Directives have recently been subject to a revision. On 17 July 2012, the Commission adopted a Proposal for a Regulation on clinical trials on medicinal products for human use³. The revision will simplify the rules for conducting clinical trials and ensuring a high level of patient safety.

In the context of clinical trials, relative effectiveness systems are designed to provide evidence to healthcare decision-makers on the benefits and risks of medicines and therapies. These systems compare drugs, medical devices, tests, surgeries, or ways to deliver health care with alternatives already existing on the market. Defining the relative effectiveness of clinical trials is complex. No common understanding of relative effectiveness systems exists among Member States. In order to overcome this barrier, the Working Group of the High Level Pharmaceutical Forum on Relative Effectiveness was set up in 2005 under the High Level Pharmaceutical Forum⁴. It laid the foundation for defining the concepts of efficacy and effectiveness of medicines. The Forum supports Member States in applying relative effectiveness systems as a means to contain costs and to reward innovation. Relative effectiveness assessment systems are relatively new for many Member States and rather complex. Nevertheless, their contribution to the assessment of effectiveness and safety of medicines is encouraging. They help identify the most valuable medicines, both in terms of clinical efficiency and cost-effectiveness and will help set a fair price for these medicines⁵.

Once medicines are placed on the market they continue to be monitored to detect any unsafe impacts they might have and to take action where necessary (by withdrawing them from sale, changing their use etc.). This monitoring is called pharmacovigilance. EMA plays a pivotal role in analysing the benefits and risks of new therapies and also ensures continued monitoring of products once they reach the market.

¹ Directive 2001/20/EC on Clinical Trials, available at:
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>.

² Directive 2005/28/EC on Good Clinical Practice, available at:
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>.

³ Proposal for a Regulation on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, available at:
http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf.

⁴ More information on the Pharmaceutical Forum is available at:
http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/index_en.htm.

⁵ More information on the Working Group on Relative Effectiveness (2005) is available at:
http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf.

The EU pharmacovigilance legislation has been subject to a major review, that led to the adoption of new legislation in 2010. The new legislation, Regulation (EU) No 1235/2010⁶ and Directive 2010/84/EU⁷, became applicable in July 2012. The 2010 legislation strengthens and rationalises the system for monitoring the safety of medicines on the European market. It improves patient safety and public health through better prevention, detection and assessment of adverse reactions to medicines.

The new pharmacovigilance legislation refers to the possibility of asking the marketing authorisation holder to conduct post-authorisation efficacy studies (PAESs), complementing efficacy data that are available at the time of the initial authorisation⁸. To determine the situations in which post-authorisation efficacy studies may be required, the Commission is mandated to adopt, by means of a delegated act, measures supplementing the provisions of Directive 2001/83/EC and Regulation (EC) No 726/2004.

The revised pharmacovigilance legislation significantly widened the tasks of the European Medicines Agency (EMA). It is currently facing the challenge of strengthening the review of product safety at both pre-approval and post-marketing stages. To finance these activities, the revised legislation provides for fees to be charged to marketing authorisation holders. It is expected that such fees will enable the EMA to conduct high quality assessments.

At a more strategic level, the European Commission has released at the beginning of 2013 the 'Investing in Health' document⁹ which establishes the role of health as integral to the Europe 2020 strategy¹⁰ and advocates evaluating and modernising current health policies to optimise their effectiveness and efficiency.

⁶ Regulation (EU) No 1235/2010 on pharmacovigilance, available at:

http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf.

⁷ Directive 2010/84/EU on pharmacovigilance, available at:

http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf.

⁸ European Commission, Delegated Act on Post-Authorisation Efficacy Studies, Replies to the Public Consultation, Brussels, SANCO/D5/FS/ci D(2013) 396156, available at:

http://ec.europa.eu/health/files/pharmacovigilance/2013_pc_paes/summary_public_consultation.pdf

⁹ European Commission, Commission Staff Working Document, Investing in Health, SWD (2013) 43 final, Brussels, available at: http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf.

¹⁰ More information on the EU2020 Strategy is available at: http://ec.europa.eu/europe2020/index_en.htm.

2. PROCEEDINGS OF THE WORKSHOP

2.1 Introduction

2.1.1 Welcome and opening – Alojz PETERLE (MEP)

Alojz Peterle, Member of the Environment, Public Health and Food Safety (ENVI) Committee and Co-chair of the Health Working Group, welcomed the attendees and the speakers of the workshop. In his introduction, he highlighted that the question of effectiveness of medicines and therapies is getting more and more attention. He said the development of a systematic approach to evaluate new drugs and therapies could improve the performance of European health systems.

Mr Peterle reminded the audience of the aims of the workshop, stating that the focus of the discussion would be on the issue of efficiency, efficacy and effectiveness of medicines and therapies. He also underlined that the debate over healthcare systems should be based on a patient-centred approach. He reflected that patients are more concerned with how drug and treatments work and what they cost, rather than a discussion of the ideologies and terminology of healthcare.

He then introduced the panellists and extended apologies from his co-host Ms Glenis Willmott (MEP) who was unable to attend as a co-chair and Dr Marcus Müllner who was unable to attend as a speaker.

2.1.2 Presentation of EC document "Investing in Health" (2013)

Mr Tapani PIHA, Head of Unit, e-Health and Health Technology Assessment, DG SANCO, European Commission

Mr Piha started his presentation by providing an overview of the European Commission's work relevant to the issue of effectiveness of healthcare systems. He specifically referred to an important document that sets the policy framework in this area: 'Investing in Health'¹¹.

The document was published by the European Commission in February 2013 as part of the Social Investment Package¹². It was presented by DG SANCO Commissioner Tonio Borg to the Ministries of Health in March and by DG SANCO Director General Paola Testori Coggi to the ENVI Committee in June. Upon its publication and presentation, the document received great attention from all stakeholders and policy makers. 'Investing in Health' establishes the role of health as part of the Europe 2020 initiative and argues that efficient spending on health can promote economic growth.

¹¹ European Commission, Commission Staff Working Document, Investing in Health, SWD (2013) 43 final, Brussels, available at: http://ec.europa.eu/health/strategy/docs/swd_investing_in_health.pdf.

¹² The Social Investment Package is an integrated policy framework which takes account of the social, economic and budgetary divergences between Member States. It focusses on: a) Ensuring that social protection systems respond to people's needs at critical moments throughout their lives. b) Simplified and better targeted social policies, to provide adequate and sustainable social protection systems. c) Upgrading active inclusion strategies in the Member States. More information is available at: <http://ec.europa.eu/social/main.jsp?catId=1044&langId=en>.

Mr Piha also highlighted that the document not only focuses on the amount of budget invested in the EU healthcare systems, but also encourages their reform.

The document underlines the importance of taking action by ensuring that investments in health systems are effective and sustainable over time. Although budgetary constraints for healthcare expenditure were already building up before the economic crisis took place, the current crisis sharpened the need to tackle challenges common to all our systems. These include the ageing population (which influences morbidity and mortality patterns) and the rising impact of chronic diseases. These challenges have led to an increasing demand for healthcare in areas previously not considered as health-related.

Given these new trends, a greater need to focus on efficiency gains was highlighted which, according to Mr Piha, should come from the structural reform of healthcare systems. Mr Piha stressed the importance for new reforms to take place and concentrate in establishing more sustainable healthcare systems whilst also guaranteeing universal access to high quality healthcare services.

Mr Piha then outlined the specific actions proposed in the document 'Investing in Health'. He mentioned, for example, the reduction of unnecessary hospital and specialist care and unnecessary procedures, through the making better use of health technology assessment, and increased use of generic medicines. Even though it is responsibility of the Member States to undertake reforms centred on the organisation and delivery of health services, the European Commission has an important role to play. The European Commission is active in the area of improvement of health systems through initiatives that help Member States work together and benefit from each other's work. Mr Piha gave three examples here: the creation of an expert panel on investment in healthcare systems; an information sharing network, through which technical results can be exchanged and health technology assessment tools shared; and the eHealth area, which has massive potential and can help better integrate health systems and make them less centred on hospitals. He also drew attention to how structural funds may be used for health investments.

In his concluding remarks, Mr Piha highlighted that both the EC document 'Investing in Health' and the Directive 2011/24/EU on patients' rights in cross-border healthcare¹³ should clarify the entitlements to public healthcare for patients. He finally added that these two instruments also improve the efficiency of healthcare systems by pooling clinical expertise across borders; and by enabling Member States to work together.

¹³ Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:en:PDF>

2.2 Efficacy and safety of new drugs and new therapies

2.2.1 Efficacy and/or effectiveness

Dr Francesco PIGNATTI, Head of Oncology, Haematology and Diagnostics at European Medicines Agency (EMA)

Dr Francesco Pignatti started his presentation by introducing the two terms, efficacy and effectiveness, and by exploring the gap between them in practice. The definitions of the two concepts were already agreed several decades ago and have been validated in different fora including more recently the EU High level Pharmaceutical Forum (October 2006)¹⁴.

Efficacy in medicine is defined as the extent to which an intervention or a drug does more good than harm under ideal circumstances, while effectiveness is defined as the extent to which an intervention or drug does more good than harm when used in real-world circumstances.

Dr Pignatti used the example of a phase 3 trial to develop this point. It is a randomised control trial that tries to enrol a narrowly selected population where all factors of variability, co-morbidity etc. are kept to a minimum (and these trials tend to be made up of patients that are in generally good health). The objective is to maximise the chances of the drug demonstrating its benefits.

The problem in the current debate is that such efficacy trials cannot be carried out at the post-approval phase. Post-approval is where effectiveness trials are actually more interesting since they see how the drug is working in practice. Effectiveness trials are conducted with a broader population of people (often older than the efficacy trial) that may not be rigorous in following all the procedures for taking a drug and who may present all sorts of other complicating factors like co-morbidity. Such trials are open to greater variability stemming from genetic differences, environmental differences (for example if the patient takes the medication with food) different ages etc., as well as non-biological and behavioural factors (e.g. not taking the drug for a long enough period). The wider population and increased variability may therefore erode the efficacy of the drug, making it perform less well than during the efficacy trial. Side effects may also manifest themselves more during effectiveness trials.

Dr Pignatti went on to explain how these differences are faced in the legal framework under which EMA approves drugs. He clarified that at the stage of approval of a drug only efficacy trials are taken into account, including the concept of risk-benefit under ideal conditions. Carrying out effectiveness trials is not strictly required by EMA procedures at the stage of approval of a drug. Effectiveness trials are by nature more oriented to the post approval phase.

¹⁴ More information on the EU High level Pharmaceutical Forum is available at:
http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/index_en.htm.

Dr Pignatti went on by presenting some figures from the EMA Annual Report¹⁵. After the drugs are approved, new data might show that in practice effectiveness is actually lower than the efficacy observed in the pre-approval trials. EMA has put in place a number of procedures through which the concerns over safety or the balance of risk-benefit of a medicine can be tackled, for instance the so called 'referrals' procedures. There are also different ways in which the gap between efficacy and effectiveness could be reduced. For example, trial data should be made as open as possible at the pre-approval stage. In addition to this, the new pharmacovigilance legislation¹⁶ has given new tools for asking for efficacy trials post-authorisation. The EMA is in the process to developing ways in which this legislation could actually be implemented.

In conclusion, Dr Pignatti considered that, despite the fact EMA does not have a relative comparative effectiveness test when assessing medicines, regulators should modify the licencing approach in more adaptive ways. For example, restricted trials could be progressively broadened throughout the drug life-cycle. In this context, regulators could offer better information on treatments to prescribers and patients. Regulators can also promote the better use of registries of medicinal information and focus more on the results of pragmatic and effectiveness trials.

2.2.2 The need for comparative efficacy

Dr Jonathan CYLUS, Technical officer from European Observatory on Health Systems and Policies, London (UK)

Dr Cylus began by stating that his presentation would focus on the need for comparative efficacy. He would investigate the reasons why such evidence is needed and how it could be made more valuable.

He explained that doctors normally choose a drug for their patients based on developed clinical evidence. Given that there are many different drugs that treat the same condition, the clinical evidence that is available is often not sufficient for the doctors to understand whether the selected drug is the best solution for the patient.

With the aim of exemplifying this concept, Dr Cylus then presented two studies that came out in the New England Journal of Medicine two weeks ago¹⁷. These studies were looking at two drugs for diabetes patients to see whether or not they had cardiovascular outcomes. In both cases the studies looked at the two drugs Alogliptin and Saxagliptin compared to a placebo. Dr Cylus explained that a placebo control trial is the purest way to know whether a drug is having an effect. However, from a doctor perspective, this is not sufficient. Even though in both cases the drugs of choice performed better than a placebo, it did not provide doctors with the information to choose between the two drugs.

Dr Cylus stressed at this point the need for good evidence that allows comparison between these drugs. This concept, described as 'comparative efficacy' or 'relative efficacy', analyses how good interventions are compared to other existing interventions under ideal conditions.

¹⁵ EMA (2012), Annual Reports 2012, European Medicines Agency, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2013/04/WC500142077.pdf.

¹⁶ Regulation (EU) No 1235/2010 on pharmacovigilance, available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf.

¹⁷ Study 1: NELM (2013), Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes <http://www.nejm.org/doi/full/10.1056/NEJMoa1305889>; Study 2: NELM (2013), Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus <http://www.nejm.org/doi/full/10.1056/NEJMoa1307684>.

There are different factors that can be compared, for example safety, tolerability as well as mortality. On the contrary, costs cannot be compared as they normally differ by country and health systems.

Then Dr Cylus argued that comparable information is needed not only by the healthcare providers and the patients, but also by manufactures, regulators and payers that can benefit from having more access to this comparative evidence. Each of those health systems actors has a role and different interests in the process of putting a drug on the market. All actors would be able to do their job better if comparative evidence is provided to them.

Research has shown that both in the EU and the US only one half of the drugs that is given the approval by the regulators really have comparative evidence that shows how well they perform compared to other drugs. In order to address this lack of information, payers have to generate the evidence themselves based on phase 3 trial data¹⁸. The problem faced by payers is that they can only get a summary of aggregate data and data that are not assessed relative to individual patients. In this context, they are forced to make a determination about whether a drug is worth paying for or not, based on incomplete data. Moreover, providers must start prescribing these drugs without having clear evidence that the drug is going to be more beneficial to the patient than existing drugs.

Dr Cylus offered some solutions to improve access to this comparative information. Given that it is very expensive and unrealistic to compare every new drug to every existing similar drug on the market, the first step is for consistent trials that compare a new drug to a comparator and to a placebo. The data from these could be then combined together, generating knowledge on how well a drug does relative to all comparable drugs on the market. HTA agencies already use this methodology called 'network meta-analysis'. Although more comparative evidence is becoming available and enhanced cooperation between manufactures, regulatory agencies and HTA bodies has been observed, such evidence is available only on a case-by-case basis and it is not consistent.

Dr Cylus then outlined ways in which comparative evidence could be made a formal part of regulatory policy. To ensure consistency in drug assessment and comparison, he suggested that a European level agency/body should be responsible to mandate how these trials need to be conducted. Such an agency should also define the active comparators to be used to compare effectiveness so that the studies and their duration are designed properly. Dr Cylus also suggested that evidence should be made more widely and publicly available, although there would be problems ensuring a high-quality analysis of the evidence.

Dr Cylus concluded his presentation by presenting the expected effects of having more comparative data available. He argued that requiring comparative evidence to be submitted at the time of drug approval would encourage innovation. Earlier availability of information could also streamline the process, so that drugs would get to patients more quickly. Finally, greater availability of this evidence would enable doctors to make the right choice for their patients based on the actual evidence, so improving clinical outcomes.

¹⁸ Phase 3 trial is a randomised control trial that tries to enrol a narrowly selected population where all factors of variability, co-morbidity etc. are kept to a minimum. See Dr Pignatti's presentation for reference.

2.2.3 The position and role of complementary and alternative medicines

Prof Dr Erik BAARS, MD, MSc Epidemiology, University of Applied Sciences, Leiden, (NL)

Prof Dr Baars started his presentation by stating that the context for the analysis of the efficacy and effectiveness of medicine is the Evidence-based Medicine (EBM) approach. EBM is the process of systematically reviewing, appraising and using clinical research findings to provide the best clinical care to patients. In the last decade, however, EBM has become much more top-down. It increasingly regulates the medical profession, determines the availability and reimbursement of therapies and marginalises the role of clinical expertise and the patient's perspective.

Clinical decision-making does not rely solely on clinical evidence – other considerations come into play. Prof Dr Baars introduced one: a different medical approach called 'Complementary & Alternative Medicines' (CAM). CAM is a group of diverse medical and healthcare systems, practices, and products not generally considered part of Conventional Medicine (CON). One important feature of CAM is that it regards itself as a whole medical system, a holistic system. CAM treatment is often very complex and its application is highly individualised to the patient. CAM combines treatments and counselling in a fully integrative way. Accordingly, the effects of such complex treatments are often larger than the sum of its parts.

There are important differences between CON and CAM Prof Dr Baars observed. In CON, medicines usually come from the laboratories and are new isolated chemicals that travel from pre-clinical studies to clinical studies and then into clinical practice. CAM medicines often take a reverse path. They first start in clinical practice and then move to clinical studies and pre-clinical trial.

He then moved on explained that non conventional healthcare approaches may also be considered part of integrative medicine (IM). IM is in fact defined as the combination of practices and methods of alternative medicine with conventional medicine. Integrative medicine emphasizes the primary goals of the wellness and the healing of the entire person; and draws on both CON and CAM approaches, in the context of a supportive and effective doctor-patient relationship. Many individuals, healthcare providers and healthcare systems are using various CAM practices into their treatment and health promotion plans.

Prof Dr Baars presented the results of a recent literature review on the topic of effectiveness and efficacy in the context of CAM¹⁹. This review looked at priorities and methods to evaluate the clinical and epidemiological research of CAM in order to identify the basis for consensus-based research strategies. It revealed that there is no disagreement that both types of research (efficacy and effectiveness) have their own place, validity and importance. Some authors nevertheless argue that efficacy research should be prioritised over effectiveness research to legitimise the use of CAM and to help increase its acceptance. Other authors state that efficacy research that examines specific effects should not be undertaken until the overall effectiveness of the therapy in question is demonstrated to prevent misuse of scarce resources. Prof Dr Baars further explained that methodological standards of medical research can be applied to CAM research.

¹⁹ Fisher et al. (2012), Key Issues in Clinical and Epidemiological Research in Complementary and Alternative Medicine – a Systematic Literature Review. *Forsch Komplementmed*.

However, it might have to be adapted to take into account the complexity of CAM interventions. CAM-specific challenges such as a lack of standardisation of treatments and study participants must therefore be addressed.

In the IM context, for treatments that are complex and personal, both conventional and complementary medicines face similar challenges in providing evidence of their effectiveness. As a solution, the Fisher review argued that there is a need for alternative/additional methods e.g. observational studies or a mix of qualitative and quantitative studies. CAM approaches could therefore be subject to similar efficacy and effectiveness tests as CON. Another approach that could work for assessing the effectiveness of CAM is the 'Reversed research strategy'. It assesses first the whole system of care being provided and then works down to the components of the treatment and their underlying biological mechanisms.

In conclusion, Prof. Dr Baars stated that both for CON and CAM, there is a growing integration of curing disease and promoting prevention. Such an integrative approach requires more and renewed attention towards how the medical professional makes decisions as well as towards patient's preferences in clinical practice and clinical studies. He added that there is an increased need for pluralism in study design and better resourced studies. This requires, however, better funded and more clinical practice trials that are adapted to the complexity of CAM.

2.2.4 First round of questions and answers

With the participation of António Fernando CORREIA DE CAMPOS, (MEP)

Before opening the floor for questions, Mr PETERLE noted that the experts' presentations had demonstrated the increasing importance of measuring effectiveness of medicines and therapies. He then welcomed his colleague António Fernando CORREIA DE CAMPOS (MEP), who is interested in the Health Working Group's activity.

A journalist based in Brussels then took the floor to ask Dr PIGNATTI's opinion on the utilisation of the network meta-analysis method as one of the way to reconcile the data.

In his response, Dr PIGNATTI explained that EMA is starting to see the potentials of this type of analysis, but there have not been any practical experience of drugs which have been approved or reviewed on the basis of this type of meta-analysis. He continued by stating that the complexity of this network meta-analysis could be a barrier for the development of trials and is always costly. Nevertheless, he thought that network meta-analysis is a very constructive tool and a valid approach for providing comparative data.

Afterwards, Mr CORREIA DE CAMPOS took the floor in order to thank the panel and the Working Group for the presentations. He expressed his disappointment to see that instead of following a more rational way, the tendency in healthcare assessment is to identify the limitation of current evaluation procedures. He recognised network meta-analysis as a very attractive tool. He asked, given that HTA agencies already use it, whether the EMA has anticipated the possibility of having a more rational and standardised common approach to network meta-analysis.

Answering this question, Dr CYLUS clarified that he did not argue that the network meta-analysis should be used to determine the approval at the EU regulatory level. He rather stressed that it is a very useful tool to understand how a new drug fits into the current market where other drugs are already available. Thus, given that these methods are already being used by HTA agencies, it is extremely important to make sure that the evidence that such bodies are using is consistent.

He continued by stating that a European level agency is needed (whether the EMA or another) to enable comparability. There are issues to be faced when using the network meta-analysis approach (e.g. they use different trials). Moreover, it is not possible to combine data from different studies unless they are comparable and consistent. Such a European agency could mandate such requirements.

Another participant from the audience took the floor and summarised the main findings of the previous intervention: that better rules on the conducted trials should be in place as well as more transparency on the results of such trials should be ensured. Taking into account these priorities, he raised his concerns that the application of such stricter rules would potentially impede research and innovation.

Dr CYLUS replied that any rule on trials should be malleable and depend on what the trial itself is trying to accomplish. He stressed once more the importance of having some common ground to ensure comparability of trials, otherwise no gain is achieved.

Dr PIGNATTI also intervened on the subject of trial design. He highlighted the importance of avoiding designing trials to suit different users (e.g. regulators, HTA etc.) He explained that there is lot of common ground between HTA and regulators in their approach to effectiveness evaluations. Then he cited the advice from the Pharmaceutical Forum that whatever evidence results from the regulatory environment should be readily usable by the HTA. This is a positive example and the advice also suggests to regulators, HTA and companies what type of evaluations to carry out.

Mr PETERLE also asked two questions to the panellists. The first question was addressed to Prof. Dr BAARS. Mr PETERLE asked whether in Europe patients who have to pay themselves for healthcare are choosing a complementary medicine approach (CAM).

Mr PETERLE then asked if there is scientific evidence available that demonstrates negative effects of the interaction of several drugs taken at the same time.

Prof. Dr BAARS replied by explaining that people are increasingly using CAM. In general there has not been sufficient evidence to understand the cost-effectiveness of CON and CAM. Nevertheless, in general, there is evidence that demonstrated the increased use of CAM medicine.

Dr PIGNATTI addressed Mr PETERLE's second question by explaining that the EMA requires substantial information from drug companies about how a drug is metabolised and the factors that can influence its performance, taking into account that concomitant medications can influence some of the parameters. Nevertheless, it is impossible to carry out studies on every possible combination. Furthermore, EMA has a reporting system for the rapid reporting of drugs' side effects. More than the regulators, the patient-doctor relationship plays an extremely important role here to ensure that patients adhere to the information given on drug use and that they understand when it is unwise to combine therapies or medications.

Finally, Jerome BOEHM from the eHealth and Health Technology Assessment Unit of DG SANCO, made some remarks on the overall discussion. He stated that it is true that Member States, including payers, HTA bodies, regulators etc. are increasingly interested in a coordinated and integrated research and regulatory process for the development of pharmaceutical products. Secondly, he pointed out that a comprehensive review of the effectiveness of all therapies- including the performance of medical devices - had not been taken into account during the session. The European Commission is committed to ensure that all such evaluations focus not only on drugs but also on medical devices and health interventions.

2.3 Access to effective medicines and therapies through relative effectiveness policies

2.3.1 Useful, superfluous, unnecessary and dangerous drugs

Ms Lidija GAJSKI (MD), Croatian Association for Patients' Rights, Zagreb, (HR)

Ms Gajski began her presentation by outlining the three uses of medication: curative (e.g. antibiotics), symptomatic (e.g. sedatives, anti-allergy treatments) and preventive (e.g. vaccines). She made some reflections on the effectiveness of these three types of medications. While there is no doubt on the effectiveness of both curative and symptomatic drugs, the need and the effectiveness of preventive drugs - those drugs that are given to the people without any symptoms of disease - is less clear.

Ms Gajski then reviewed in more details the efficacy of a number of drug categories. She noted that their effectiveness in clinical practice was often less than the efficacy shown in laboratories. She gave the example of trials of antihypertensive, hypolipidemics and aspirins drugs that aim to prevent cardiovascular disease. She explained that these trials demonstrated the reduction or minimisation of cardiovascular diseases in only one out of eight patients with high cardiovascular risk treated. In the same vein, other trials showed that the effects of these drugs are even lower when tested on healthy population with low cardiovascular risk. Ms Gajski cited other drug categories which have similarly low or even insignificant effectiveness, some chemotherapy treatments for example. She also claimed that the preventive effects of vaccines is also unknown as proper studies have never been performed into their effectiveness. Finally, Ms Gajski argued that very limited effects have been found for other preventive drugs such as antiviral drugs and for hormone replacement therapy, where no benefits are seen in the prevention of future disease.

Ms Gajski pointed out how the pharmaceutical industry plays a critical role in this lack of effectiveness and safety. She claimed that evidence demonstrated that the pharmaceutical industry manipulates trials to make their products look better than they really are. Studies analysing the relationship between the outcomes of the clinical trials and their sponsorship sources found that those trials financed by the pharmaceutical industry are four to five times more likely to produce results in favour of the sponsoring company than studies funded by other sources.

Ms Gajski argued that the results of these studies demonstrated how the pharmaceutical industry has coloured our perception, overestimating for example some drug benefits and creating new clinical disease states. Antidepressant drugs, for instance, formerly prescribed for severe forms of depression only, now have 12 different indications, including minor anxiety disorder(s). Disease severity and prevalence is also exaggerated by the industry. Some sponsored epidemiological studies argued, for example, that a simple flu was a threatening disease or that 1/12 of mankind is affected by the hepatitis virus. Such biased studies expand disease definition and have contributed to the creation of 'new diseases' for physical conditions that used to be considered a normal part of life (osteoporosis or menopause for example) and for psychological states of mind, for example, social anxiety disorder which in the past were considered part of a person's character (i.e. A 'shy' person is now a sick one).

As a consequence of these distortions, Ms Gajski noted two changes in our thinking on health: 'medicalisation', where normal life processes are transformed into phenomena requiring treatment; and a shift from curative medicine to 'preventive medicine', where treatments are taken now to prevent or minimise possible future diseases. She argued that we are often being overdosed, over-treated and over-diagnosed.

We are also harming ourselves through the increasing use of medications which are often insufficiently tested, may pass through inadequate approval processes and are subject to poor post-marketing surveillance. In her views, pharmacological prevention is a concept created by the drug industry which has in the past few decades opened up new markets and reaped enormous profit opportunities from healthy populations. This is a distortion and abuse of what a beneficial preventive approach should be and, most importantly it creates medical, economic, social and cultural harm.

Ms Gajski argued that a conflict of interest between the pharmaceutical industry and regulatory agencies lay behind this distortion. She said that better regulation was needed to improve the relationship between industry and regulatory agencies. Regulatory agencies licence drugs on the basis of a relatively small number of studies and studies often of a short duration. She identified the influence that the pharmaceutical industry has on the regulatory bodies as one of the causes of this distortion. Ms Gajski also denounced the post-marketing surveillance procedures, which are inadequate in catching treatments that may be harmful. She explained that only 5 to 20 % of side effects are normally reported to the regulatory agencies because no sanctions for non-reporting are in place and because physicians are insufficiently educated and sensitive to the issue.

In her conclusion, Ms Gajski proposed that, to achieve a rational drug policy, the conflict of interest over research and its private funding- which could bias trials - should be eliminated.

2.3.2 Second round of questions and answers

Before opening the floor for questions, Mr PETERLE commented on the session. As a legislator, he understood the importance of regulation for ensuring effectiveness and safety of medicines.

Mr CORREIA DE CAMPOS took the floor and made some observations on the second session of the workshop. He expressed his disagreement with some parts of Ms GAJSKI's presentation. While he agreed on some points - the increase of medicalisation, the abuse of hospitalisation and the distortions to which preventive medicine has been subject - he argued that the efficacy of vaccines has been well demonstrated over the past decades (e.g. in reducing the incidence of infectious diseases such as tuberculosis in the last 100 years). He also stressed that he is aware of different findings compared to those presented by Ms GAJSKI regarding the beneficial effects of chemotherapy. He argued that an extension of life expectancy after initial treatment has been demonstrated by different studies and is highly visible in a number of patients. He also mentioned the work undertaken by the WHO - which is considered an authoritative source and an independent body by all - on the effect and safety of antidepressants. He suggested that the occidental approach of seeking to cure disease, as opposed to an oriental approach of adapting to it, remained important.

Ms GAJSKI answered these remarks by explaining that she used to share the same opinion as Mr CORREIA DE CAMPOS. However, the results of several studies carried out in the last 10 years, persuaded her and other researchers and investigative journalists to change their minds on this topic. She also clarified that the statistics presented are backed-up by a huge amount of literature that could not be cited/referenced in a 10 minutes presentation. The findings of this body of literature demonstrated that almost half of the medicines and treatments are unsafe or unnecessary.

2.3.3 Conclusions

At the end of the workshop, Mr Peterle expressed his gratitude to all speakers for the very interesting debate and fruitful discussion. He pointed out that, even though the sessions have been marked by a few disagreements between experts and the audience, these have fuelled the debate with a view to finding shared solutions.

He finally informed the participants that other workshops will be organised by the Health Working Groups within the ENVI Committee before the end of the mandate. He also highlighted the importance of maintaining a specific working group on health in the future.

He finally extended gratitude to the ENVI Committee Secretariat and the Policy Department A-Economy & Science for the organisation.

ANNEX 1: PROGRAMME

WORKSHOP

Effectiveness of Medicines and Therapies

Wednesday, 18 September 2013 from 13.00 to 14.45
European Parliament, A1G-2, Brussels

**Organised by the Policy Department A-Economy & Science
for the Committee on the Environment, Public Health and Food Safety (ENVI)**

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, SANCO, European Commission.

Part 1

Efficacy and safety of new drugs and new therapies

13.10 - 13.20

Efficacy and/or effectiveness

Dr Francesco PIGNATTI, Head of Oncology, Haematology and Diagnostics at European Medicines Agency (EMA)

13.20 - 13.30

The need for comparative efficacy

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

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

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

ANNEX 2: SHORT BIOGRAPHIES OF EXPERTS

Mr Tapani Piha

Tapani Piha works as a 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 first in 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 Francesco Pignatti

Francesco Pignatti graduated as medical doctor at the University of Rome La Sapienza.

In 1995 he became research fellow at the EORTC Data Center, Brussels, Belgium, where he was involved in numerous activities including clinical trial design, conduct, analysis, and reporting. In 1997 he became Medical Advisor for the Gastrointestinal Tract Cancer Cooperative Group, and Brain Tumor Cooperative Group.

In 1997 he obtained a Master of Science degree in Biostatistics from the University of Limbourg, Belgium.

In 1999 he joined the European Medicines Agency (EMA) in London. Since 2009 he holds the position of Head of Oncology, Haematology and Diagnostics in the Unit for Human Medicines Development and Evaluation.

Dr Jonathan Cylus

Dr 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. His 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, Dr Cylus was an economist at the Centers for Medicare and Medicaid Services 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. Dr Cylus 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 (ESCOMP). 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).

Ms Lidija Gajski

Ms 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. Ms 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.

Ms 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).

ANNEX 3: PRESENTATIONS

Presentation by Dr Francesco Pignatti



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Efficacy- Effectiveness

Addressing the gap

Francesco Pignatti, MD

Workshop on "Effectiveness of Medicines and
Therapies"; European Parliament, 2013

An agency of the European Union



Efficacy versus effectiveness

Efficacy is the extent to which an intervention
does more good than harm under **ideal**
circumstances

Effectiveness is the extent to which an
intervention does more good than harm when
provided under the usual circumstances of **health**
care practice

Definitions by the EU High Level Pharmaceutical Forum (Oct 2008)



EUROPEAN MEDICINES AGENCY

Legal Framework

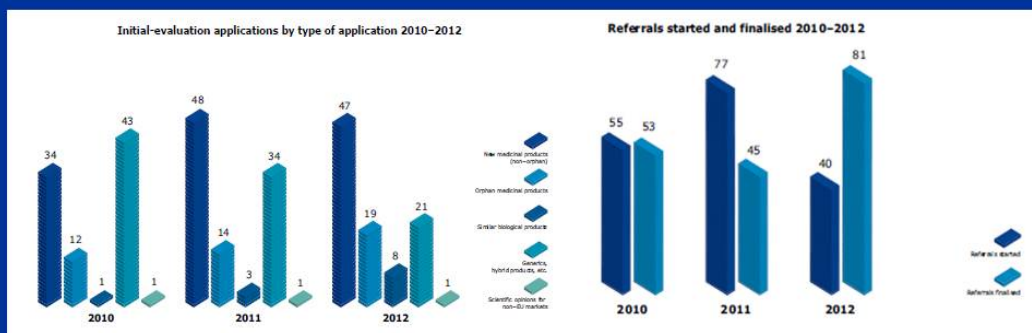


- Must establish positive benefit-risk balance to obtain marketing authorisation
 - Based on objective criteria (quality, safety, efficacy)
 - No notion of (relative) effectiveness
 - In general, clinical trials shall be done as controlled clinical trials randomised versus placebo and an active control
- Refusal of a marketing authorisation the quality, safety or efficacy have not been demonstrated

Regulation (EC) No 726/2004, Directive 2003/83 (EC)

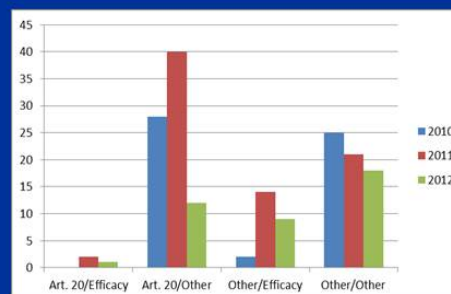
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Applications and Referrals to EMA



EMA Annual report 2012

A minority of “efficacy” referrals on centralised products (Art. 20/Efficacy)



4



EUROPEAN MEDICINES AGENCY

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”)

5



EUROPEAN MEDICINES AGENCY

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...”

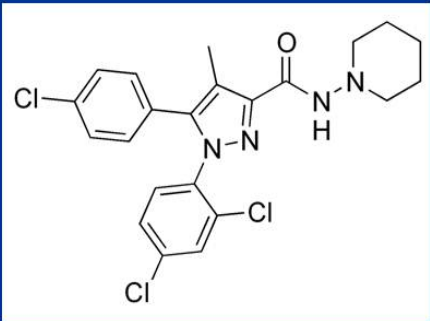

risk of experiencing the adverse mental effects are higher in patients with comorbidity”)

6

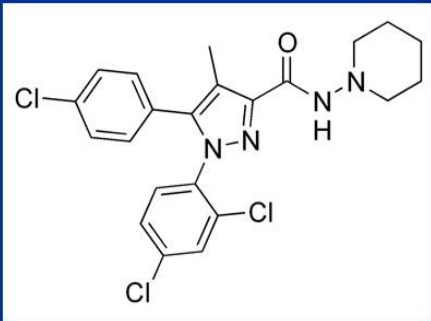

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What does, and what does not change?

before ← licensing → after

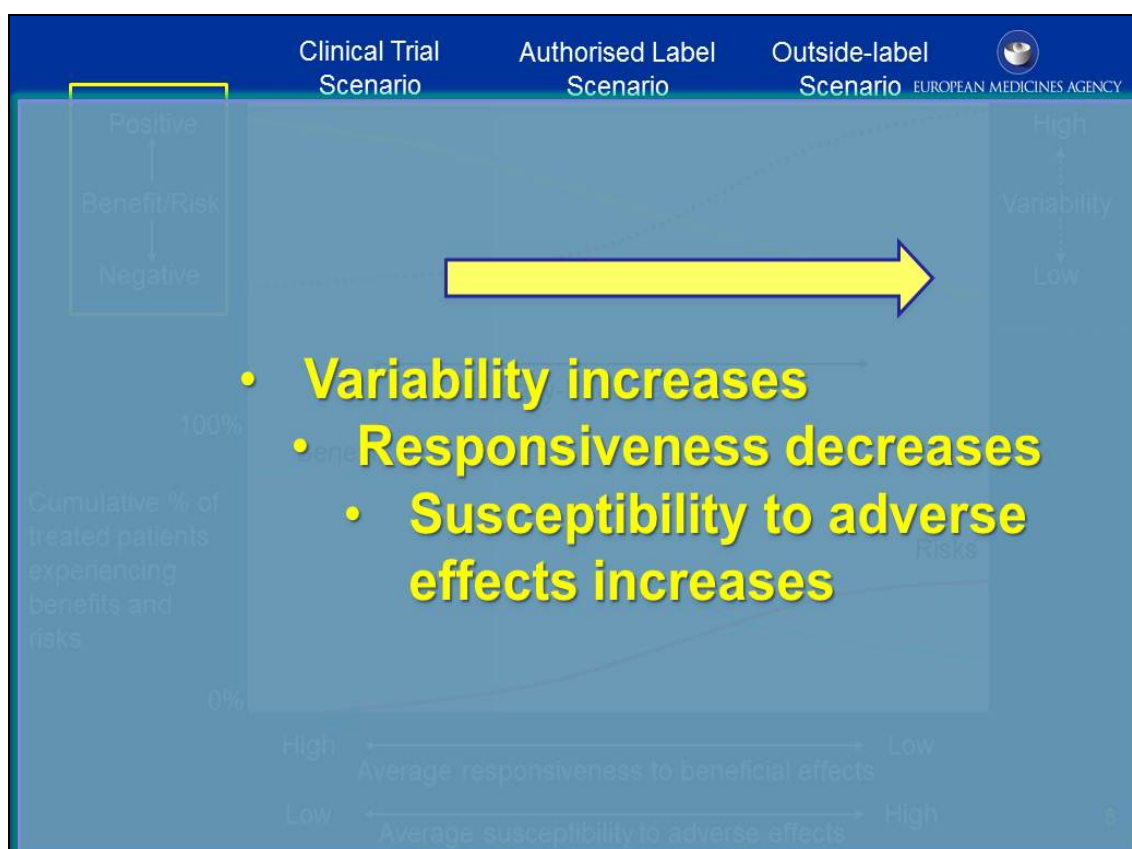



?

A problem of uncertainties and variability

7





EUROPEAN MEDICINES AGENCY

Sources of variability in drug response

Biology

Behavior

Genomics	Environment	Physician prescribing	Patient adherence
Patient's genomic makeup	Co-morbidity, baseline severity of disease, altered physiological states, external factors	Inappropriate prescribing, prescr. to non-responders, medication errors	Poor adherence to prescribed drug regimen, non-persistence; "drug holidays"; overdosing
PD: Trastuzumab Abacavir PK: Codeine: resistance / tox. (CYP2D6)	PD: Insulin and stress /activity PK: increased absorption with fruit juice	Cerivastatin; Gemfibrozil; Mibefradil;	Anti-hypertensive, anti-infective drugs

9



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Ways to bridge the gap

- Regulators to focus more on **external validity** of clinical trial results (pragmatic-/ effectiveness trials)
- **Continuous assessment of the benefit-risk** balance of medicines throughout their lifecycle, including real life
 - Post-authorisation efficacy/**effectiveness studies**?
 - Are we making the most of **registries**?
- Optimise **healthcare delivery** and information about medicines (prescriber and patient-adherence directed interventions)
 - Measure the usefulness of risk-minimisation
- Pharmacogenomics etc., and perhaps, **new licensing approaches**

10

Thank you



Acknowledgements: Hans-Georg Eichler (EMA); Xavier Kurz (EMA)

Presentation by Dr Jonathan Cylus



The **red** pill or the **blue** pill? The need for comparative efficacy

Jonathan Cylus
18 September 2013

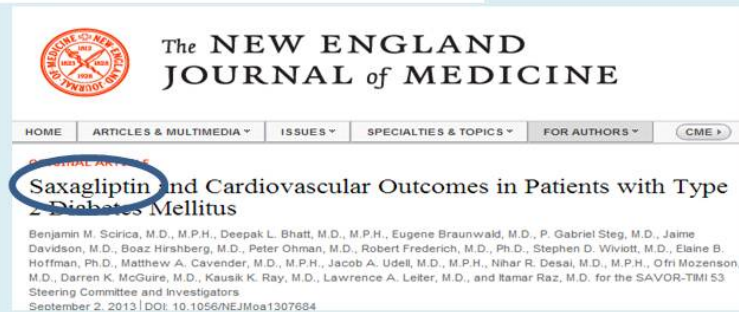


“What is the drug of choice for condition X?”

- 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



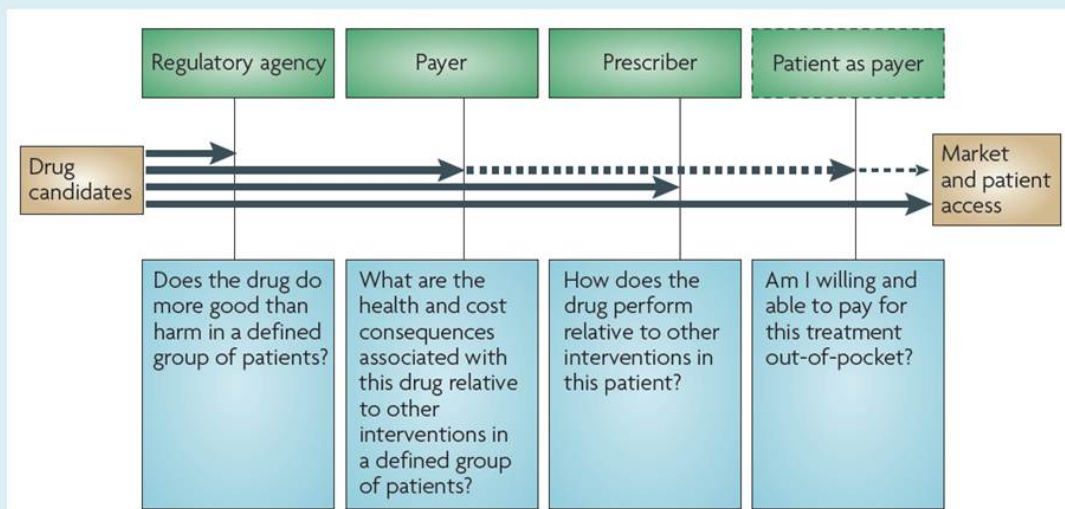
- Why not compare costs?
 - Costs differ by country, health system

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

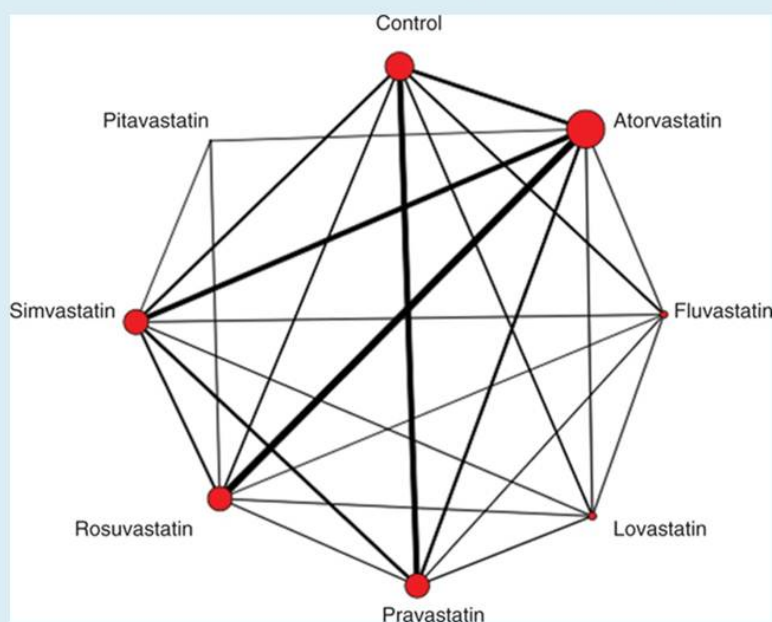
* van Luijn, et al (2007) Availability of comparative trials for the assessment of new medicines in the EU at the moment of market authorization, British Journal of Clinical Pharmacology

** 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 olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *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



Workshop "Effectiveness of Medicines and Therapies".
18 September 2013. European Parliament, Brussels, Belgium.



The position and role of complementary and alternative medicines

Prof. Dr. Erik W. Baars

MD, MSc Epidemiology, PhD
University of Applied Sciences Leiden, Leiden, The Netherlands
Louis Bolk Institute, Driebergen, The Netherlands
ESCAMP, Freiburg, Germany

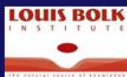
Efficacy and effectiveness

- Clinical research
- Efficacy trials (explanatory trials): determine whether an intervention produces the expected result under ideal circumstances
- Effectiveness trials (pragmatic trials): measure the degree of beneficial effect under "real world" clinical settings
- Continuum



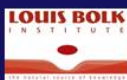
Context: Evidence-Based Medicine

- 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



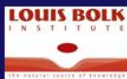
Context: Evidence-Based Medicine

- 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"



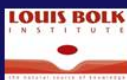
Complementary & Alternative Medicine (CAM)

- 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.



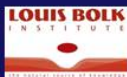
Complementary & Alternative Medicine (CAM)

- 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



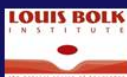
Complementary & Alternative Medicine (CAM)

- 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.

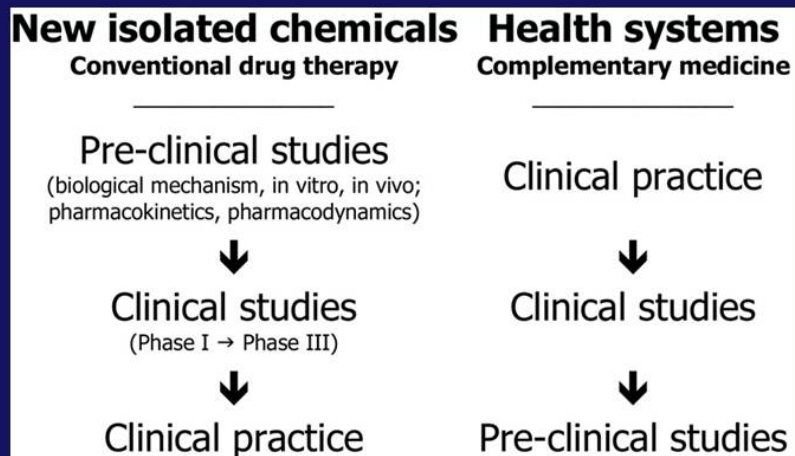


CON and CAM: traditional differences

- | | |
|--|--|
| <ul style="list-style-type: none">• CON:<ul style="list-style-type: none">– <i>Worldview:</i><ul style="list-style-type: none">• biomedical/ humanistic model– <i>Health:</i><ul style="list-style-type: none">• default situation• machine– <i>Disease:</i><ul style="list-style-type: none">• breakdown of the machine– <i>Treatment:</i><ul style="list-style-type: none">• group oriented guidelines/ protocols• fighting disease• requires external resources | <ul style="list-style-type: none">• CAM:<ul style="list-style-type: none">– <i>Worldview:</i><ul style="list-style-type: none">• holistic/ spiritual model– <i>Health:</i><ul style="list-style-type: none">• result of organism activity• wholeness/ balance– <i>Disease:</i><ul style="list-style-type: none">• expression of system imbalance– <i>Treatment:</i><ul style="list-style-type: none">• complex individualized interventions• health promotion• requires internal resources |
|--|--|



CON and CAM medicines: different pathways in development



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



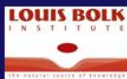
CON and CAM: integration in Integrative Medicine

- 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



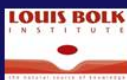
CAM: efficacy and effectiveness

- 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*



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.



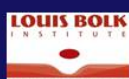
CAM: efficacy and effectiveness

- 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



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



CAM: efficacy and effectiveness

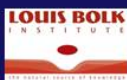
- 'Reversed research strategy' for assessing CAM, e.g.:

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



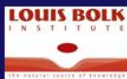
CON & CAM: similarities relevant for efficacy-effectiveness

- 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



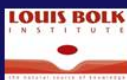
CON & CAM: similarities relevant for efficacy-effectiveness

- 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



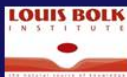
Conclusions

- 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.”



Thank you for your attention!

- **More information:**

- Email: baars_e@hsleiden.nl
- Websites: www.hsleiden.nl/lectoraten/professorship-anthroposophic-healthcare
www.louisibolk.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.



Presentation by Dr Lidija Gajski

Useful, superfluous, unnecessary and dangerous drugs

Lidija Gajski
Croatian Association for Patients' Rights

Workshop on "**Effectiveness of Medicines and Therapies**"
18 September 2013, European Parliament, Brussels

Medication

- **curative** – antibiotics
- **symptomatic** – analgetics, bronchodilators, antiulcer th., sedatives, anti-allergy drugs ...
 - substitutional - hormones (insulin, thyroxin), vitamins (B12, D) minerals (Ca, Fe)
- **preventive** – hypolipidemics, hypoglycemics, antihypertensives, antiplatelet agents, drugs for osteoporosis, vaccines

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**

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

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

Moore, JAMA 2012

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

Abraham, BMJ 2002

**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

	<u>Primary interest</u>	<u>Secondary interest</u>
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

DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT ECONOMIC AND SCIENTIFIC POLICY **A**

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- Industry, Research and Energy
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