

Assessing Claims for Efficacy for Herbal Medicinal Products by applying EBM and Meta-Analyses

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Summary

The paper starts with a short description of the present state for assessing claims for efficacy. The revolutionary scientific changes and organisational changes which are presently occurring are described. The basics of evidence-based medicine (EBM) are outlined and the goal of EBM to dominate medicine is mentioned. The essentials of Meta-analyses such as the levels of evidence are shown and an example for a successful Meta-analysis is given. Frequent objections against the results of Meta-analyses of herbal medicinal products are described. Claims for herbal medicinal products are justified by many general reasons. Positive and negative evidence from the available Meta-analyses are shown. The costs for broad implementation of the best available evidence in the population are unsustainable. The overall conclusions include that Meta-analyses are an interesting option for companies in the health care field. They are useful for several purposes and health policy in Europe should acknowledge Meta-analyses as valuable instruments. The will of patients and consumers not to use classical therapy alone and to accept some risk in using herbal medicinal products instead must be respected. Governments and the European Union have to place the will and the preferences of the people at their highest priority and should change the procedures and laws in favour of herbal medicinal products.

Introduction

The evaluation of what is true in medicine and how patients should be treated has always been controversial. Drug laws in many countries have been implemented providing rich experiences in a variety of cultural settings. These experiences show that regulation is culture-specific and different in many

countries. Regulation has been changed after drug catastrophes markedly (Contergan, blood contamination by HIV) and this might occur again.

The state of art during the last decades was focussed on randomised controlled clinical trials (RCTs). However, there are huge differences between the situation in RCTs and treating the ordinary outpatient (selection, life situation of patients) and the results of RCTs cannot be transferred to ordinary outpatients.

Old drugs are usually safer because we know more about them. Weighting benefit versus risk, both measured with meaningful and valid instruments, is the decisive criterion and the core of most modern drug laws. It is not efficacy alone. The balance between benefit and risk for patients is decisive. It is generally accepted that the same principles and procedures must be applied for all drugs, HPMs as well as ordinary clinical or high tech therapeutic procedures. One should strive to have not too many different standards for phytomedicine, perhaps two or three, not more.

The state of art in assessing claims for efficacy is presently undergoing revolutionary scientific changes. Our knowledge is exploding and is changing very quickly. The human genome project and related new techniques provide completely new kinds of drugs. The epidemiology of a disease, its prevalence and incidence in the population and the real outcomes in the population, define what providers have to deliver: life expectancy, quality of life, number needed to treat and so on. There are huge differences between guidelines and the situation in the real world. Only a fraction of the population is treated according to the best available standards.

Doctors no longer decide on treatments alone. Patients are in the driver's seat. They determine, what they want and what type and extent of risks they are willing to take.

Old scientific principles are reformulated in new ways: evidence based medicine (EBM), Meta-analyses, decision analysis and health technology assessment (HTA). Costs are becoming more important: life time costs and cost-efficiency cannot be the only criteria to optimise medicine. In Germany and the EU there will remain the solidarity principle for the weaker parts of the population.

The state of art in assessing claims for efficacy is also currently undergoing revolutionary organisational changes: Public opinion gets more impact. All players in the health care system are taking a more active role: patients, physicians, governments, society, the media, and other organized groups in the health care system. Social processes between interfering groups are becoming more important. Treatment according to good standards must be available not only for the rich, but also for the poor. This vision has great impact, even when it cannot be realised. The differences in life expectancy and quality of life between the poor and the rich will remain huge or increase.

The national laws are changed by the European Commission. More centralised and unified admission procedures are introduced. This has been shown by several papers in this conference. The worldwide cooperation between the FDA, Europe and other countries is increasing. Globalisation changes the processes of drug development and drug licensing. The direction is towards a single worldwide market and the same or very similar licensing procedures all over the world. On the other hand it is quite clear that drugs are culture-dependent. Drinking red wine in the South of France or Italy in the summer is different from drinking brandy bottles during the winter in Norway.

The internet and the unlimited rapid exchange of

information allows electronic admission procedures. It gives access to all available information about drugs to users, the public, the regulatory bodies and the government. The truth about the information on drugs in the www cannot be assessed easily by the users. One can find every nonsense on drugs in the www and the user remains helpless. Simultaneously old markets are disappearing and new markets are evolving for herbal medicinal products and botanicals, food supplements and life style drugs.

Evidence Based Medicine.

Evidence Based Medicine (EBM) is the conscientious, explicit and reasonable use of the best available external scientific evidence for decisions in the management of individual patients(1). EBM in the practice of medicine is the integration of individual clinical expertise with the best available external evidence from systematic research.

EBM is focussed on the individual patient and on problem oriented learning of MDS. This is expensive and must be done in medical schools and during life long training of MDS, it is not a problem of the industry. On the other hand EBM is focussed on the system. EBM also aims at an evidence-based supply of medical care for the population. It tries to optimise the processes between the players in the health care system. Economic considerations are of high importance in EBM. EBM is supported by the Cochrane Collaboration acting in many countries and represented in Germany by Deutsches Cochrane Zentrum in Freiburg (2,3,4).

EBM acknowledges only therapies which are objectively proven. It requires that only drugs or therapeutic procedures with proven efficacy should be paid by sickness funds or health insurance. However, only one third of the procedures and cures in medicine are investigated according to the state of art. One third is partly investigated and one third is gambling, we know nothing about it according to the state of art.

To clear the notions a little further, one has to separate

the principle of EBM (to pay only what is proven) and its support by the Cochran Organization from the methods we have. Study methods are methods for RCTs, for cohort or case control studies, for epidemiologic surveys or for reporting adverse effects. Statistical methods are hypothesis testing, modelling, Meta-analyses and so on. The principle of EBM and the use of methods are influenced by the political processes in organizing health care.

The costs of the best available external evidence for the major chronic illnesses in the population are very high and cannot be paid by existing funds.

The goal of EBM is to dominate medicine. It has been developed toward a philosophy of rational clinical decisions. EBM requires that the rational decision process in practical medicine follows its criteria and rules. EBM is a paradigm requiring the dominance in the management of patients. It is necessary to apply and to implement medical procedures according to its concepts. EBM also requires to dominate medical research according to its principles.

You can like it or not: EBM tries to dominate medicine via its paradigm, which is not so new after all. Such comprehensive notions usually get weaker after some time. The same will occur with the overall importance of EBM.

Meta-Analyses

Meta-Analyses are different from EBM and only partly connected to it. Meta-Analyses summarise and condense several studies into one statement. They increase the chance for relevant results by using the combined information and larger numbers. Statistical significance is easier to achieve. When one increases the numbers, any small difference must become “significant”, even when it is just a chance effect. Meta-analyses provide an estimator for the average result and its confidence limits.

In order to fulfil this miracle, Meta-analyses have to adhere to strict requirements and must follow a study

plan. They start with a careful literature review. The literature usually overestimates the effects because of “Publication Bias”. With weak studies the principle “Garbage in Garbage out” applies.

The enclosed studies must be randomised, must have the same inclusion/exclusion criteria and must use the same outcome variables. Criteria for inclusion of studies must be defined as well as the statistical techniques used. Information on patient data or certain variance statistics must be available. These data are often not published and their collection is time consuming and requires patience and some resources, if one can get them at all.

Meta-analyses are a well established and well accepted methodology. Even regulatory agencies have recommended them recently. Meta-analyses are cheaper than new studies. Meta-analyses allow hypothesis testing, provided they are done according to the state of art and RCTs of high quality are available. Meta-analyses can provide new hints on efficacy, side effects and indications besides hypothesis testing. This can be an input for the direction of further research and for the scope of licensing. Sensitivity analyses can show whether and how much the results vary depending for instance on quality of studies or time of publication.

Meta-analyses end with one of five levels of empirical evidence. Level 1: Highest possible evidence: at least one systematic review based on Meta-analyses of several RCTs. Level 2: At least one large RCT of high methodological quality. Level 3: Several open studies without randomization but of high methodological quality like prospective cohort studies or case control studies. Level 4: More than one non-experimental study of higher methodological quality. Level 5: Weakest possible evidence: Opinions and convictions of “authorities”, expert panels of consensus conferences without additional empirical support, descriptive studies.

The highest possible evidence - Level 1 - has been reached by several Meta-analyses of RCTs of

phytotherapeutic preparations using appropriate outcome measurements. This evidence is comparable to the best empirical evidence in other well-known fields of medical therapy.

Level 1 and level 2 correspond to group A as described in previous papers yesterday (well established use), level 3 and level 4 correspond to group B as described (well-established use or new traditional use directive) and level 5 corresponds to group C, which is no evidence.

What should be the minimum level of evidence from a scientific point of view? I think we have three options. My preference would be level 3. When one relaxes the requirements, it would be level 4. When one wants stronger requirements, it would be level 2. Finestine, one of the most critical authors proposes to confine outcome measurements to total death or to focus only on a few studies which are methodologically good.

Phytotherapy in mild to moderate BPH might serve as an example for Meta-analyses. A well known study was published by Wilt et al. in JAMA 1998 (5). The objectives were to conduct Meta-analyses regarding the therapeutic efficacy and safety of *Serenoa repens* (Dwarf Palm) in men with symptomatic benign BPH. 18 RCTs involving 2939 men were selected. The treatment was at least 30 days. Results compared to Placebo: *Serenoa repens* decreased urinary tract symptom scores (IPSS), decreased nocturia and improved peak and mean urinary flow rates and residual urinary volume. Results compared to Finasterid: *Serenoa repens* decreased urinary tract symptoms Scores (IPSS) and improved urinary flow.

These results were significant at least at the 5 percent level. We can be pretty sure about these reductions in Lower Urinary Tract Symptoms (LUTS) by *Serenoa repens*. Adverse effects due to *Serenoa repens* were mild and infrequent. Erectile dysfunction was more frequent with Finasterid. The authors conclude that *Serenoa repens* compared to Finasterid produces similar improvements in urinary tract

symptoms and flow measures, has fewer adverse treatment effects and costs less. This example shows that the efficacy of a plant extract can be proven by Meta-analyses.

Frequent objections against the results of Meta-analyses of herbal medicinal products are:

- (1) The content of the preparations is different and varies highly. Combinations of therapies are widely accepted in RCTs like Chemotherapy + Radiation versus surgery. Why should such studies be not accepted in HMPs, where the content is also different? I think different content does not matter so much. When there is significant efficacy in meaningful endpoints, the results are on the conservative side because averaging the content dilutes the effect size.
- (2) The causative mechanisms are not known exactly and are different. There are only rare cases in genetic diseases where we know the mode of action exactly. I do not think that it is necessary to have similar mechanisms of action or the same content of drugs in order to perform an RCT and to prove the efficacy with relevant outcome measurements. The fruit salad principle is correct, when fruit salad is consumed and not apples and pears separately. In phytomedicine mixtures of plants are consumed and not single substances. Obviously one can compare different lipid lowering drugs and bypass surgery in an RCT and achieve significant differences. This is accepted by the scientific community. Since Meta-analyses are based on RCTs, these requirements for every single RCT should hold also for the results of Meta-analyses of the same RCTs.
- (3) Are the results clinically relevant? The term clinically relevant is used widely in many publications. An improvement of 20 percent or more is generally accepted as clinically relevant. When the results of Meta-analyses of

herbal medicinal products show better improvements than 20 percent, they should be accepted as clinically relevant. Moreover, clinical relevance is shown by the patients themselves. The overall satisfaction of patients with phytotherapy is well known and demonstrated by their willingness to pay without reimbursement. Quality of life as judged by patients is also improved.

To summarise the frequent objections against Meta-analyses in phytotherapy: There are many examples with improperly performed Meta-analyses and misleading results. However, there are also examples in phytomedicine with waterproof results.

Results and Conclusions

Claims for herbal medicinal products are justified by general reasons: The percentage of adverse effects is generally lower. The quality of life is generally improved. Long term therapy is well tolerated. Herbal medicinal products are better accepted by patients and doctors than more aggressive regimens. More aggressive regimens can be shifted for some time. Self medication contributes to the empowerment of the individual patient, which is an important concept in Public Health. Herbal medicinal products are generally cheaper than other regimens. The potential risks are smaller. Therefore the requirements for proof of effectiveness and market access can be less rigid.

The positive evidence from available Meta-Analyses and evidence based medicine (EBM) shows that several Meta-analyses of RCTs and observational studies prove the efficacy and large population effectiveness of herbal medicinal products according to level 1, the highest possible level of evidence. Adverse effects of herbal medicinal products are rare and the risk-benefit relation is generally positive for first line treatment. Herbal medicinal products are cheaper and might be more cost effective than other therapeutic approaches. Herbal medicinal products are often accompanied by improved quality of life. Patients are willing to pay by themselves for herbal medicinal products without reimbursement.

Therefore watchful waiting combined with herbal medicinal products is a serious option in the treatment of many diseases.

We also have negative evidence from available Meta-analyses and Evidence Based Medicine (EBM). The long term reduction of symptoms and the long term evaluation of complications is open. The consequence should be only short term use. In patients with serious illnesses the possibility for missing life saving therapy or improvements by using herbal medicinal products is existent and has to be considered. It is very important, that a patient could die or be harmed more than necessary by using phytotherapy and not other therapies which are proven effective. This danger can only be mitigated by formulating clear conditions for change to other therapeutic options like more aggressive regimens from high tech or classical medicine.

The overall costs for the use of herbal medicinal products are generally higher, since patients pay on their own and the overall budget for drugs is rising. Whether the financial benefits are larger or smaller remains open and must be analysed separately for every drug. A caveat should be placed here. The methodology for economic analyses of drugs is context sensitive and in comparison to the methodology for RCTs rather new. The results can depend on the view of the sponsor and the view of the authors. With the same input data different groups can end with different results.

Managing all patients with diabetes, hypertension and severe risk of myocardial infarction according to the best available evidence following the principles of EBM would approximately double the present total drug budget. Neither governments nor health insurance nor sickness funds are able to pay the population costs for the broad implementation of EBM without rationing. Rationing is on the other hand not accepted by the voters and the population. A substantial increase or a doubling of the percentage for health care costs of the gross national product is also unlikely. During the next decade a complete

change of the health care systems in Europe or muddling through are the options. This is not an optimistic outlook. But it opens chances for phytomedicine and HMPs.

Nobody has a crystal ball. I personally expect a phase of expansion for HMPs during the next years. Different ways of getting a license and the preference of patients will support this trend. This phase of expansion could last 5-10 years and will be followed by a phase of consolidation. A contraction could occur, when a major drug catastrophe could rightly or wrongly be attributed to phytomedicine.

Meta-analyses are an interesting option for companies in the health care field to carry through their goals. Meta-analyses are a well established and well accepted methodology to get evidence on effectiveness. They are cheaper than new studies. They can provide meaningful hints for possible directions for registration and research.

Meta-analyses are useful for getting herbal medicinal products on "positive lists", for getting herbal medicinal products out of "negative lists", for proving therapeutic benefits which are "larger than petty" and for supporting "well established use" and "traditional use" according to new proposals which are discussed in the EU.

Therefore health policy in Europe should acknowledge Meta-analyses for these purposes and should not talk so much about EBM, the costs of

which are unsustainable for the population and for the total drug market.

The will of patients and consumers not to use classical therapy and to accept some risk in using herbal medicinal products must be respected. Drug companies should investigate the preferences of their consumers and use the results for changing health policy in their countries. Governments and the European Union have to place the will of the people at their highest priority. They should therefore change the procedures and laws in favour of herbal medicinal products.

Literature

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