Osteopathy and Evidence Based Medicine

Analysis of Studies Investigating Benefits of Osteopathy as Treatment of Back Pain

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1. Summary

Back pain is one of the most common reasons for office visits to physicians in industrialized nations. Besides personal disabilities, back pain is the reason for considerable non-productivity time and therefore has a substantial economic impact. The causes of back pain are as multifaceted as its treatment modalities. Therefore, patients, therapists and health care providers ask the valid question which of the therapies is really beneficial for the patient.

Evidence based medicine evaluates therapies in clinical studies according to scientific criteria. After introduction of the history and concept of evidence based medicine, in this thesis I will discuss the results of the most relevant clinical studies, reviews, and meta-analysis over the last 15 years that examined whether spinal manipulation or osteopathic intervention is beneficial for back pain patients.

In summary, the results do not provide evidence for pain reduction or improved function by these interventions. Preliminary indications of a slightly improved cost-utility-effectiveness haven been explained by placebo effects.

An explanation of this result may be that osteopathic manipulation itself is a multi-faceted treatment modality with poorly defined and standardized methods, which is a major weakness on the way to demonstrate efficacy in the grading system of evidence based medicine.

More basic research including novel methods of molecular biology and systems biology as well as imaging techniques to quantify physiological changes after osteopathic treatment seems absolutely essential to demonstrate any specific effect of osteopathy.

2. Introduction

Evolutionary survival of a biological species is mainly determined by genetic adaptation. However, today, life-time and life quality of a human being is substantially co-determined by medicine. And today's medicine is coined by scientific research. Thus, science increases the chances of survival of both the human species and the individual.

A fundamental principle of science is to reduce the enormous complexity of nature and life processes by taking them apart in order to better understand causal relationships (i.e. when A

then B) of the parts. Similarly, medicine today in theory and practice is dictated by the scientific principle of dissection and, at the same time, it is the product of scientific research. In the clinics, the success and efficacy of a treatment or a drug is measured by the increase in lifetime and life quality. While lifetime is indeed a measurable quantity, life quality has to be somehow parameterized. Evidence based medicine (EbM) demands that decisions for a particular therapy are based on clinical studies that demonstrated its efficacy.

The concept of EbM, however, is not necessarily reconcilable with the philosophy of a holistic medicine such as osteopathy, which focuses predominantly on treatment of the individual patient and the resulting subjective experience. The knowledge derived from treatment of an individual patient has been rarely quantified and transferred to other patients. This can only be achieved by establishing general principles derived from the results of scientific studies (Resch, 2004).

Contemporary conventional medicine relies more and more on a health care system that is based on efficacy and effectiveness demonstrated in clinical studies. Therefore, it appears indispensable that osteopaths establish solid evidence and prove benefits of osteopathic manipulation. (Heard, 2006). Research in osteopathy following the EbM criteria is absolutely necessary due to enormous political, economical, and social pressure, and for consideration of osteopathy in future treatment guidelines.

Ian Drysdale even argues that the development and survival of osteopathy in future medicare depends on whether osteopathic research succeeds to receive attention by scientists, academics, and the critical public. Well-designed clinical studies demonstrating efficacy, cost effectiveness and a favorable risk benefit ratio of osteopathy will be an essential contribution to achieve this goal.

Up to date, a large number of studies have addressed the effects of functional-structural methods such as osteopathy on back pain patients (Kuchera, 2005).

In my master thesis, I have investigated the results of the most important publications and reviews of these studies over the last fifteen years to find out whether there is any scientific evidence in favour of osteopathic treatment of this condition.

3. Evidence based medicine and osteopathy

3.1. Basics of evidence based medicine

Prof. Edzard Ernst, who holds the first Chair of Complementary and Alternative Medicine (CAM) at the University in Exeter, United Kingdom (UK), regards the emergence of evidence based medicine as a milestone in the history of medicine.

> "While physicians were previously outrageously inefficient and blind to damage, the clinical trial is used routinely for the development of new methods these days, and there is a consensus among the experts, that evidence-based medicine is the key to effective health care. The evidence-based medicine provides physicians a secure basis for decision-making, as long as they are provided with the most reliable information, and thus serves the patient, because it increases the probability of getting the appropriate treatment." (Ernst and Singh, 2008) (p.40)

3.1.1. Evidence based medicine

Evidence based medicine (EbM) is a direction in medicine demanding that with each medical treatment, patient-oriented decisions are expressed explicitly on empirically proven effectiveness.

The concept of 'evidence-based medicine' was shaped in the early 90s by David Sackett and Gordon Guyatt at McMaster University, Hamilton, Canada, in the Department of Clinical Epidemiology and Biostatistics. David L. Sackett refers to it as: "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al., 1996). Ideally he interprets it to be a combination of individual clinical expertise as well as the best available external clinical evidence from systemic research. Only the careful integration of the two parts allows a good physician to decide on the right treatment and procedure for an individual patient.

> "The practice of evidence-based medicine means integrating individual clinical expertise with the best available external evidence from systemic research {...} good doctors use both [...] and neither alone is enough." (Sackett et al., 1996)

3.1.2. Importance of evidence based medicine

In clinical practice, this means the integration of **internal evidence** (expertise and expert report) with the best available **external** clinical **evidence** from systemic research (clinical trials and their publication), and **patient preferences** (desires and expectations for high-quality, safe and low cost treatment). Hence, treatment recommendations and treatment guidelines for both the individual patient as well as for groups of patients with the same disease, as well as for entire populations, can be developed.

The decision on the treatment of patients therefore no longer lies in the hands of an individual, but is derived from the knowledge of experts, which is constantly updated with new research findings, and the values and expectations of a patient. One hopes that the way of decision, cynically described as 'eminence based' (i.e. top down decision of the chief physician) within the community of physicians, can be overcome. The easier access to information and a better appreciation of the values and wishes of the patient are regarded as key to this development.

> "Key developments since the recognition of EBM have included enormous advances in ease of accessing and understanding information, {...}, and the increasing emphasis on patient's values and preferences in clinical decision making." (Montori and Guyatt, 2008).

3.1.3. Development of evidence based medicine

This process of decision-making however, requires research and evaluation of subject-oriented literature. Today, search machines in the Internet (world wide web) offer the ability to quickly retrieve original scientific articles in a specific journal, on a particular topic, field of research, or author. (Montori and Guyatt, 2008). In principle these articles are available to everyone, although private users generally have to pay fees for access to the full articles to the publishing journal.

For physicians and health care providers there are two substantial challenges: (i) to find the time to keep up to date with the progress and new findings in medicine in all the publications, (Sackett et al., 1996) and (ii) to interpret correctly the results of the clinical studies in the primary journals and find out which study is indeed solid.

> „Medical and health policy training must continue to evolve, allowing clinicians and politic makers to successfully differentiate truly evidence-based sources of information and interpretation of information, from those that are not." (Montori and Guyatt, 2008).

Meanwhile there are services offered to assist in the evaluation of published studies and their conclusions. For instance, the Premium Literature Service (PLUS) such as the ACP Journal Club originated by McMaster University.

> "The ACP Journal Club not only highlights selected articles with high methodological quality and potential relevance but also offers structured abstracts that document methodological quality criteria, which allows readers to evaluate the validity of the results. In addition, these services present pertinent results transparently and offer independent commentary." (Montori and Guyatt, 2008)

It has already become essential due to the flood of publications that research not only consults primary literature in form of original articles, but also reverts to secondary literature such as reviews.

One of the most important organizations for the creation, updating and dissemination of these review papers is the Cochrane Collaboration, a worldwide network of scientists and clinicians, who aim to follow the assessment of current therapies according to strict methodical criteria. It works as a nonprofit organization and the collaboration is voluntary. They now operate Cochrane centres in thirteen countries, which are supported by health authorities, universities, or research funds in coordination, organization, public relations as well as in education and training (Wikipedia).

EbM itself is a young and evolving science, with the aim of evaluating the quality of published medical data and consequently improving it. EbM is not devoted to conduct clinical trials, but to the systematic use of their results.

3.1.4. Qualification criteria in evidence based medicine

Classification criteria have been established to evaluate studies of the efficacy of a therapy and to create treatment guidelines. Levels of evidence are thereby hierarchically arranged according to validity criteria.

The Agency for Quality in Medicine (ÄZQ/AQuMed) in Germany suggested the following criteria and ranking. The evidence of efficacy is obtained from several (level 1) or from at least one (level 2) randomized controlled trial. Evidence is achieved by a methodically well-designed but not randomized study (level 3) or from clinical reports of individual cases (level 4a). The opinion of recognized experts, who assess based on clinical experience, has the weakest evidence (level 4b).

Similar classifications were established in the USA by the Preventive Services Task Force and in England by the National Health Service (Wikipedia). However, there are some differences in the formulation, which may be too simple or too contrived and complicated, and are therefore interpreted differently and the cause of confusions. For instance, in some cases proper assessment of review articles has been difficult.

> "Other reviews, which used different quality rating scales, rated the studies less favorably and believed that meta-analysis would be inappropriate because the trials were heterogeneous in terms of design, type and duration of back pain, acupuncture treatment protocols, and outcome measures" [Cherkin, 2003 # 4].

In order to unify the different classification systems and to include additional issues such as relevance and feasibility, an international working group called "GRADE Working Group" (Grading of Recommendations, Assessment, Development and Evaluation) has been establishing a new system since the year 2000. The new GRADE system for assessing the

evidence and development of recommendations is now gaining international recognition and is supported by the World Health Organization (WHO), the Cochrane Collaboration and many others.

> "GRADE offers four levels of evidence quality: high, moderate, low, and very low. Randomized trials begin as high quality evidence and observational studies as low quality evidence. Quality may be downgraded as a result of limitations in study design or implementation, imprecision of estimates (wide confidence intervals), variability in results, indirectness of evidence, or publication bias. Quality may be upgraded because of a very large magnitude of effect, a dose-response gradient, and if all plausible biases would reduce an apparent treatment effect." (Guyatt et al., 2008)
> „The GRADE process includes an important evolution in EBM: the definition of quality of evidence and the components that determine quality including study design and study limitations, consistency, precision, and the extent to which the evidence directly applies the patients, interventions, and outcome of interest." (Montori and Guyatt, 2008)

3.1.5. The randomized controlled study as gold standard of evidence based medicine

3.1.5.1. History of RCT

One of the first clinical trials documented in the history of medicine was conducted by the ship's doctor James Lind on board of the Salisbury in 1754. In the age of discoveries (15th to 18th century) scrutiny was one of the major reasons for death amongst seamen. For a trial J. Lind grouped 12 seamen ill by scrutiny who "*were as similar as I could get them"*(…) in six groups of 2 patients each who received all the same diet and daily application of either 1.1 litre cidre (group 1), 25 drops sulfid acid (group 2), 6 spoons vinegar (group 3), ¼ litre sea water (group 4), 2 oranges and lemons (group 5), or a dose of garlic, mustard and perubalm (group 6). He found that only the two seamen of group 5 who got citrus fruits recovered already after 6 days in contrast to all others (Lind, 1753).

The first documented experiment, which was controlled by a kind of placebo was conducted in the year 1784 by the famous scientist Benjamin Franklin. In that age Franz Mesmer claimed that in the human body there is a "*fluid*" which he could influence from distance. There was a commission with Benjamin Franklin that performed a series of test experiments. So in one room women were "*mesmerized"*, with the right or wrong information that Franz Messmer was sitting behind a curtain. Franklin could prove that it depends only on the women's believe the mesmerist would be there, and so he refuted the effect of the new method (Wikipedia).

In 1920 Prof. A.B. Hill and R.A. Fisher introduced randomization as a basic principle of experimental study design. The first application took place in agronomy where divers kinds of

fertilizer or cereal were distributed randomly to parcels of land for to avoid that assignment happens biased on parcels with bad sole quality (Armitage, 2003).

A study about treatment of pulmonary tuberculosis with streptomycin conducted on behalf of the British Medical Research Counsil is often cited as the first randomized controlled trail. (Porter, 2000)(p.531). The results were published in 1948 in the British Medical Journal.

3.1.5.2. RCT today

Today the randomized and placebo-controlled clinical trial (RCT), which also should be double-blinded, is regarded as gold standard for the evaluation of therapy. For evaluation of drugs it is an absolute must.

According to Ernst and Singh the seven characteristics of the double-blind trial are: (1) A comparison must be able between a control group and an intervention group. (2) Each group must consist of a sufficiently large number of patients. (3) Patients should be randomly assigned (randomized) to groups. (4) The control group must be administered a placebo. (5) Control group and treatment group must have the same conditions. (6) The patients must be blinded in the sense that they do not know which group they belong to. (7) The therapists must be blinded in the sense that they do not know if a patient is being administered a drug or a placebo (Ernst and Singh, 2008)(p.89f).

Prof. Karl-Ludwig Resch, director of the Balneology and Spa Medicine Research Institute of Bad Elster, claims that to date, there is not a more accurate and reliable method of identifying data regarding treatment relevant questions than the RCT.

> "Until today, no other method is known with which statements can be obtained, which are more accurately and more reliably conveyed to future patients. However, here again, one can only optimize the probability of having done the best possible - there is no guarantee in a given case" (Resch, 2004).

Moreover, Prof E. Ernst notes that *"the RCT is not the best methodology, {...} but at present no better one exists"* (see in (Chaitow et al., 2004)). He admits that clinical research often means that compromises are necessary and one is confronted with challenges, obstacles and problems. The perfect study simply does not exist. In their book, "Healthy without pills", Ernst and Singh speak of the impossibility of replacing this type of clinical study in medical research, which deal with the question of the efficacy of a therapy.

> "These kind of clinical trials are irreplaceable when one conducts medical research. Although the results from other types of testing and other data can be included, these are generally considered less convincing when it comes to the crucial question: Does a treatment have an effect on a particular disease?" (Ernst and Singh, 2008) (p.90).

RCTs assess effectiveness of a technique or a therapy within an ideal population of patients as homogenous as possible at a clearly defined point in time. As such it is quite unrealistic. It is the kind of study that strives for being most scientific in the sense of objectivity, standardization and reproducibility. Randomization and blinding substantially account for that. However, for many clinical situations, these features are impossible or difficult to achieve for several reasons including ethic considerations, feasibility, kind of intervention, number of subjects and cost factors. The results should mainly improve the extern validity of a medical intervention to allow generalization. Nallamothu speaks about *"efficacy"* in this context (Nallamothu et al., 2008).

For manual therapies a placebo treatment and double blinding is almost impossible. Instead, groups of patients with and without intervention are compared. Study design and data analysis, however, underlies standardized methodological approaches. Often the studies impose high costs and commitment of resources and the results refer to a selected homogenous population at big medical centres. Small sample size of groups, however, reduces the chance to discover small treatment effects or rare complications. Special logistic and ethical challenges have to be considered for studies with less common, but life-threatening diseases.

It is also difficult to assess complex and multifaceted therapies with RCTs. The large number of variables in the daily clinical practice is an almost insurmountable hurdle for the feasibility of RCTs with strong evidence. In a critical comment to a publication of a meta-analysis by Assendelft and colleagues (Assendelft et al., 2003) that showed no benefits of spinal manipulation in the treatment of low back, Jan Dommerholt wrote:

> "There are too many relevant variables in clinical practice which determine the effectiveness of modalities. These variables on the one hand include knowledge, training, clinical background and experience of the practitioner, on the other hand the pathology, age, sex, fitness stage and other personal characteristics of the patient. Possibly they contain amongst others also issues like effect of confidence or expectations of the patient to the therapy, avoidance of fear and self-effectivity, interrelational and psychosocial issues as well as socioeconomic and medical judiciale/juristic/legal factors. Practically no modality or treatment approach who was recently used by practitioners in health care could bear up against the strong rules of RCTs" (J. Dommerholt in (Chaitow et al., 2004)).

For this reason, he thinks that the RCT should not necessarily be considered as the unique or preferred method to examine effectiveness or efficacy of clinical modalities, although they are *"wide spread and in general accepted as 'best evidence'"* (J. Dommerholt in (Chaitow et al., 2004)).

3.1.6. Further clinical studies on evidence of efficacy

While a RCT provides the best objectivity of the efficacy and effectiveness of a treatment, it does not necessarily provide the clinician with all the information needed for the choice of the most adequate treatment of a patient. For this, according to the principles of EbM, he has to collect and interpret all available information of all relevant clinical studies. Pragmatic clinical trials and observational studies might deliver additional information, provided they are of high quality.

3.1.6.1. The pragmatic clinical trial (PCT)

Pragmatic trial studies evaluate the benefits of therapies under more real conditions by allowing a broad range of methodological parameters and less stringent inclusion criteria for the treatment groups. Therefore PCTs are thought to show the effectiveness of a treatment rather than the efficacy provided by RCTs in an ideal but unrealistic setting (Nallamothu et al., 2008). The results of PCTs compensate for some shortcomings of RCTs. PCTs aim at a better balance between external and internal validity. As such it may provide valuable additional information. However this comes at a price. PCTs are usually more costly in terms of time and resources than RCTs.

3.1.6.2. Observational Studies

Observational studies are often described as patient-oriented data acquisition in the health care system. Observational studies are designed as purely explorative studies for the generation of hypotheses. They involve a large and divers population of patients in real-world settings. Accordingly, rare complications or minor treatment effects can be detected. They may provide important insight in the clinical context, in which often complex and multiple therapies are applied. Usually, observational studies are relatively inexpensive and timesaving. Multiple methodological approaches are available, which unfortunately, are often inconsistently applied or described. A bias in the selection (not randomized) of patients make it difficult to compare treated and non-treated patients.

Three different kinds of observational studies are introduced below.

3.1.6.2.1. Cohort Studies

A cohort is a group of individuals with common exposure to a risk factor, a prognostic factor, or a specific type of intervention. Usually this cohort is compared with one or more cohorts that have not been exposed to this factor. The groups are observed prospectively for a certain

time and the outcome of interest. From the results of the different cohorts the *'relative risk'* can be calculated (Hoppe et al., 2009).

By careful selection of individuals, an observational study can be of high quality without the delay inflicted by randomization, which may anyways not be ethically justifiable in some cases. Thus, the outcome of a cohort study may have a substantial impact on and deliver important information for decisions regarding procedures in the clinics (example: within four days after hip fracture an operation should happen in order to diminish mortality among elderly people) (Hoppe et al., 2009).

3.1.6.2.2. Case Control Study

In a case control study a group of individuals that have all experienced a similar clinical condition (the dependent variable) is compared with a group that has been free of this condition. Usually case-control studies are carried out retrospectively and are not as powerful as cohort-studies in calculation of risk probabilities and therefore rank lower in the evidence classification hierarchy. However, compared to a cohort-study, a case-control study may be favourable when the time period for observation is very long or the outcome is expected to occur rarely and so an enormous sample size would be required for a cohort study. Furthermore, case-control studies are often performed to assess adverse effects or complications of interventions such as post-surgical infections. Similar to the cohort-study, careful selection of the individuals of the control group excluding any bias and confounding factors increases internal and external validity of a case-study.

3.1.6.2.3. Case Studies as single reports or series and registries

Case studies including single patient reports or collection of related case reports (often from the same hospital) are characterized by a detailed description of the history of the patient and procedure of treatment. Therefore they are used to describe rare diseases or unusual side effects of a treatment. Such reports must be interpreted critically, since they are retrospective, biased, and come without controls. But they may give an orientation for future more ambitious scientific studies (Nallamothu et al., 2008).

The category of case studies also includes registries, which already exist in various countries for instance for the results of surgery. Centralized databases that are accessible on the Internet are useful to inform surgeons about potential complications, risk factors for bad results and special operation procedures of colleagues. For registration usually no inclusion or exclusion criteria exist. They allow a long-term observation or different kinds of retrospective

considerations. So, they are an important source of information that has been used already for the development of guidelines. And they may become even more important in the future.

Ernst and Singh are convinced that *"The scientific study is best suited to determine not only the truth in medicine, but is also the best way to help the truth receive recognition" (Ernst and Singh, 2008)(p.48).*

Open-mindedness, fairness, and transparency appear to them as the essential attributes of researchers: *"* (they shall) *remain open to potential new evidence and shall possibly revise conclusions"* (Ernst and Singh, 2008)(p.41), i.e. they should not *"layout their experiments to achieve the expected result"* (Ernst and Singh, 2008)(p.52).

The authors use the example of the nurse Florence Nightingale, who discovered in 1855 by means of accurate observation and statistics that poor hygiene condition was responsible for increased mortality in a military hospital of Scutari, to argue that *".... evidence-based medicine actually allows an outsider to get a hearing. It (the EbM) welcomes any treatment that proves to be effective, whoever is behind it, and however absurd it may seem"* (Ernst and Singh, 2008)(p.42). They most likely want to motivate the representatives of complementary or alternative medicine in particular, even if the *"idea of evidence-based medicine sometimes might seem a bit cold, confusing and intimidating to people outside the established medicine"* (Ernst and Singh, 2008)(p.40).

3.1.7. Economic aspects of evidence based medicine

Some insurance companies use the conclusions of studies according to EBM about the effectiveness of specific therapies as the basis of their policy of reimbursement of costs.

> "Some insurance companies have been very aggressive in using evidence-based arguments to deny payment for untested treatments - a circular problem, because how do you create the evidence that insurers demand unless you test the untested?" (Gorman, 2007)

In this context, it proves to be a disadvantage if methods are not or only tested sparsely, or underlie a false or an inadequate assessment.

> "The downside thereby is that studies like this (Note: meta-analysis) can be used by a third party to refuse payments, earnings, etc., even though the limitations of RCTs are well known." (Jan Dommerholt zitiert in (Chaitow et al., 2004))

The search for scientific knowledge is not only important for the communication with health care providers, but also in terms of the expectation of the patients. If nothing else, the patient requires that he or she is offered an effective method.

> "Effectiveness is important because, with few exceptions, consumers don't enjoy paying for healthcare services that fail to 'work as advertised'." (Lucas and Moran, 2006)

A reasonable enhancement represented here is the so-called 'Value based medicine' (VbM). Their studies devote a special attention to the cost-benefit effect of medical intervention. In the process they evaluate the benefits especially regarding the patient and his or her quality of life as well as length of life. Thus the parameters of cost and quality of life are in the foreground. The main instrument of VbM is the cost-utility analysis to quantify the benefits for the patient to try to match them subsequently with the standard cost.

> "The cost-utility analysis is calculated from the gain of value of benefit and from lifetime earnings of quality adjusted life years (QALYs) and is set in relation to costs (€ / QALY)." (Brown et al., 2005)

Such an approach has already occurred in some areas of traditional medicine, whereas until now, only few studies in the field of complementary medicine have addressed the cost-benefit ratio: "….costs have rarely been measured in trials of CAM therapies." (Cherkin et al., 2003)

In a meta-analysis on the problem of back pain, Licciardone and colleagues emphasize the great need to incorporate the question of costs in future studies in which osteopathy is also applied. (Licciardone et al., 2005), which he reinforced later.

> "There is a great need for research involving the costs in providing OMT for musculoskeletal conditions. {…} Cost-effectiveness analysis and cost-utility analysis are two established methods that should be used to study the cost implications of OMT." (Licciardone, 2009).

The same is actually also mentioned by Assendelft and colleagues (Assendelft et al., 2003) in their meta-analysis of back pain treatment with osteopathic manipulation.

According to Dr. Melissa Brown, an ophthalmologist and President of the Center for VbM founded in 1998 in Flourtown (USA) and member of the Institute for Health Care Economics at the University of Pennsylvania, the acquisition of further parameters opens up new possibilities to classify even less serious symptoms.

> "Noteworthy is the fact that a number of more recent clinical trials have incorporated quality-of-life instruments. Unfortunately, the more commonly utilized instruments, such as the Medical Outcomes Study Short Form-36 and Short-Form 12, the Sickness Impact Profile (SIP), the EuroQol, and others often are insensitive to milder diseases and not applicable across all specialties. Additionally, most emphasize primarily function. Unlike utility analysis, they frequently fail to incorporate all parameters (concern about family and other dependents, socioeconomic status, caregiver status, anxiety versus depression, fear of the unknown or the future, etc.) associated with health-related quality-of-life." (Brown et al., 2003)

So far, the centre for VbM has been the contact body for pharmaceutical companies, who wanted to have a neutral institution testing the application of their products in terms of economic efficiency.

3.2. Limits of evidence based medicine

3.2.1. Interpretation and meaning of RCT findings

3.2.1.1. Lack of proven benefits and lack of benefit are not the same

While a positive RCT result has conclusiveness, absence of an RCT is inconclusive and does not mean evidence of ineffectiveness: "Absence of evidence is not evidence of absence" (Altman and Bland, 1995). This reverse asymmetry seems trivial, wherefore the utility of many established medical interventions, such as life-saving measures in emergency medicine, is often not further questioned even without RCT evidence of efficacy. With a strict interpretation of EbM, many surgical methods or for example defibrillation of ventricular fibrillation, should not be applied due to lack of RCTs. But which person in need of surgery could be withheld from it for study purposes? Depending on circumstances, the implementation of RCTs is simply not ethically justifiable. For these reasons, the surgical removal of an inflamed appendix or a tumorigenic breast, were, for the longest time, not based on a touchstone of RCTs.

Only the collection of postoperative negative results such as relapses or subsequent complications led to a retrospective critical consideration of such operations. The unparalleled success story of surgery, which revolutionized medicine in the last century through the increasing technization and refinement of their instruments, would actually stand on the touchstone, if proof of utility by RCT were strictly required.

Unfortunately many of the complementary therapies are often assumed ineffective, because there is no RCT evidence of efficacy available. That means that the logically false reverse is concluded here. This may lead to the elimination of such therapies, even if they may be effective (Kienle et al., 2003).

3.2.1.2. False negative results of an RCT

Just like the lack of evidence, the negative outcome of the RCT is not a valid proof of ineffectiveness. Because the result can be false negative due to various weaknesses in a study.

> "The major weakness of the randomized trial is the difficulty for protection against false negativity." (Freireich, 1997)

"Basically no effective therapy is immune to be proven ineffective, due to formally perfect, but substantially careless studies and thus to disappear from the patient's treatment" (Kienle et al., 2003).

Even the checklist-based evaluation of a study proved to be insufficient to discover the factors that led to false-negative results, and to take them into account in the final evaluation.

3.2.1.3. Divergent outcome of an RCT

Although RCTs are designed to overcome the divergence in medical assessments, the results of several RCTs with the same question are also often divergent themselves.

> "The current debate about the sense and senselessness of mass screening mammograms exemplifies that different professional evidence-based evaluations of identical clinical trials may still yield different conclusions and even different treatment recommendations." (Kienle et al., 2003)

To acquire an extensive evaluation, systematic meta-analyses are conducted, in which the results of individual RCTs will be summarized and statistically analyzed. But even these can prove to be divergent, since they are interference-prone and difficult to assess.

> "The poor quality, inconsistent conclusions, and biases of many studies and reviews have led to confusion." (Cherkin et al., 2003)

3.2.1.4. False positive results of an RCT

Meta-analyses may possibly be assessed as false positive. The reasons lie for example in the large heterogeneity in study design regarding the inclusion criteria of the volunteers, of the outcome parameters, or of the limited number of studies included. The checklist-based evaluation of the study proved to be insufficient to discover factors that led to false negative results, and to take them into account in the final evaluation.

3.2.1.5. The "RCT Uncertainty Principle"

In physics, the famous Heisenberg's Uncertainty Principle implies that it is impossible to precisely measure the position and momentum of a quantum object simultaneously. That is, the more precisely one property is known the more blurred the precise identification of the other. The same seems to apply to the outcome of RCT. Studies with a large number of patients provide a statistically accurate result, from which one does not know to whom it applies to. In contrast, small numbers of patients in a study provide a statistically inaccurate result, from which one better to whom it applies to. In addition, a statistically accurate result for or against a measure provides no statement, whether it is the best measure at the moment,

i.e. at a specific moment in life. The findings from clinical research do not necessarily state what really is best for the individual patient (Sackett et al., 1996).

3.2.1.6. Correlation does not equal Causality

A statistical significant difference when comparing two or more parameters usually only reveals correlations. Causalities however, will remain unresolved until confounders can be completely excluded. But in a clinical trial this is virtually impossible.

> "Statistical significance alone does not necessarily imply a cause- and effect relationship, nor even an association, unless the presence of confounding factors can be eliminated" (Hoppe et al., 2009).

In contrast to clinical trials, causal relationships can definitely be derived from experimental research.

3.2.2. Significance of the publication of studies

The published studies on the effectiveness of a particular therapy are not necessarily representative of the effectiveness, because many of the negative results are not published, for example, because there is no interest on the journals' part or potential authors are inexperienced in the process of publication.

3.2.3. Non-consideration of unpublished studies

Inversely, many smaller studies are not published and thus avoid consideration. Thus, Licciardone noted in his meta-analysis of RCTs of osteopathy in patients with LBP, that the conclusions of his study could be significantly changed if the results of unpublished studies were included. He calculated a figure of sixteen studies with positive results that would have been necessary for it. However, he believes it to be very unlikely that so many studies would have been funded and conducted without being published afterwards.

> "The results of unpublished trials of OMT for low back pain may have altered significantly the conclusions of this study. (...) Historically it is highly unlikely that 16 trials of OMT for low back pain would have been sponsored, conducted and subsequently not published." (Licciardone et al., 2005)

3.2.4. EbM promotes the commercialization of medicine

The EbM promotes the commercialization of medicine, because the preparation and evaluation of RCTs may be influenced and controlled by market economy-based interests.

> "Randomized trials are immensely expensive, the cost is estimated at 5,000 to 10,000 Euros per patient. {...} Because of high costs together with a low governmental or non-profit funding, clinical research increasingly drifts into the domain of the Pharmaceutical Industry, where it obeys licensing and

> marketing interests. As a result, only therapies, which are patentable and offer financial benefit, are given priority to be explored" (Kienle et al., 2003).

In fact, costly clinical trials usually will not be funded with public money. Only some therapies and issues, for which the public interest is great enough, may be an exception.

> "Only recently has government funding for research in the area of complementary and alternative medicine become more widely available, in response to the public's interest in such treatments" (Licciardone et al., 2005).

While Ernst and Singh see a good chance especially for outsider methods to measure themselves with conventional methods in the scientific study (Ernst and Singh, 2008), the medical directors of the Institute for Applied Epistemology and Medical Methodology in Freiburg, Gunver Kienle and Helmut Kiene, indicate the *"chances of survival in the EbM-competition"* as *"definitely not equal"* (Kienle et al., 2003). Despite the potential efficacy of complementary therapies, the danger remains that, in the course of commercialization and bureaucratization of medicine, they are rationalized away. In their opinion, the bureaucratization of clinical research is possibly even responsible for the stagnation of progress, which has been emerging for some time.

> "Clinical research is characterized by high degree formalization and bureaucratization. This was recently discussed in Lancet (Horrobin, 2002) as well, as a possible cause of the pharmacological-therapeutic progress, which has been stagnant for more than 30 years." (Kienle et al., 2003)

An economic interest of sponsors may allow not only the feasibility of scientific and clinical studies, but also the evaluation of the implementing scientists.

> "Researchers funded by industry interpret their results differently and in favour of the industry product relative to not-for-profit funding." (Montori and Guyatt, 2008)

This is why respectable scientific journals require the information on sponsors ("grant support") and potential financially interested parties ("potential financial conflicts of interest") for the publication of studies.

3.3 Difficulties of osteopathy with EbM

As explicitly experiential based, osteopathy relies only exceptionally on statistical-epidemiological and formalized audit procedures. On the EbM scale of hardness of evidence (see 3.1.4.) clinical trials usually provide no hard evidence on the benefits of osteopathy (or rather a well-defined osteopathic treatment) that would fit into the Layers 1-3. At best, one could argue that osteopathy experts have assessed a particular therapy positively based on experience and individual cases, which is at the lowest level of the evidence scale. Along with

this reason, these studies are very rarely accepted for publication in renowned medical journals. Prof. Dr. Matthias Beck reaches a similar assessment of osteopathic studies as well.

> "On closer inspection, these studies almost always only have a low level of evidence as they are created on the basis of parameters, which primarily assess the health status of the patients. Accordingly, they are therefore unfortunately worthless to be accepted for publication in renowned medical journals and it is a real shame for all the hard work and energy that is thereby invested for example by enthusiastic osteopaths. Only rarely reproducible results are found in these studies, which are able to demonstrate their importance through randomized controlled and cohort studies, such as the work currently nearing completion by Jane Carreiro on the osteopathic treatment of otitis media, which was promptly accepted for publication in a prestigious medical journal of the United States." (Beck and Unverricht, 2005)

Listed below are some reasons, which pursue the question of why osteopathy pushes its limits when it comes to the benefits of osteopathic treatment, demonstrated by clinical studies. The same or similar reasons are largely applied to many complementary therapies.

3.3.1. Weaknesses in the methodology

3.3.1.1. Osteopathy as a medical intervention

An osteopathic diagnosis and treatment strategy for the treating osteopath arises less from defined pathophysiological contexts, but results rather due to the following guiding principles, which were described in 1953 by a committee of osteopaths in Kirksville (Thompson, 1953): (1) The body is a unit; (2) the body possesses self-regulatory mechanisms; (3) structure and function are interdependent; and (4) rational therapy is based on an understanding of the body as a unit of self-regulatory mechanisms and the mutual interaction of structure and function.

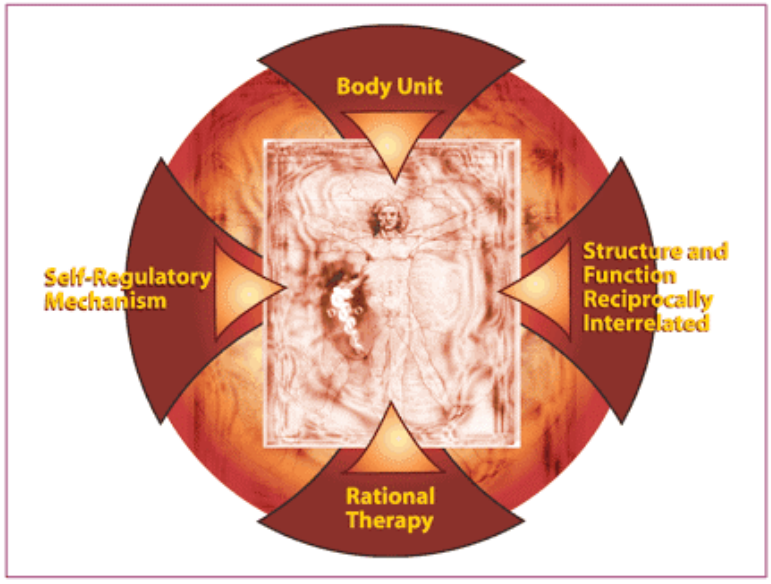


Figure 1:
The graph shows the 4 guiding principles, of which an etiological concept, a philosophy and a therapeutic technique were derived, that constitute osteopathy. In this picture the patient is presented as the Vitruvian Man by Da Vinci. (Rogers, 2005)

These philosophical principles, however, are generalities and do not give detailed instructions as to which intervention is to be used with which disease.

> "Clearly the definition of 'osteopathy' is intended to specify that it is not the diagnosis or treatment that defines 'osteopathy' but a guiding philosophy and set of principles. This brings us to the crux of the issue, for it follows from this definition that any diagnostic or treatment strategy can be osteopathic, so long as it is based on osteopathic principles and philosophy" (Lucas and Moran, 2007a).

A.T. Still, the founder of osteopathy has defined the disruption of the free flow as the cause for every disease, which is a result of the *"blockage of nerves, veins and arteries"* (Still, 2005b). This site of congestion later became known as an *"osteopathic articular lesion"* and to this day is referred to as *"somatic dysfunction"* (Comeaux, 2005). The metamorphosis of this concept reflects the effort by the osteopaths to find a common language for their examination results, which has not led to a standardized therapy yet. Behind each word, however, hides the inconsistent understanding of the pathophysiologic correlations. A better understanding of these, however, would be a necessary prerequisite, to be able to discuss the best treatment for a patient with the physicians and if necessary to be able to provide an evidence for the effectiveness of an osteopathic treatment.

3.3.1.2. Lack of objectivity of osteopathic research methods

For several years the osteopathic training is mediated by the conduct of clinical trials as the basis for diagnostic work, but its validity is partly controversial.

> "... many of the diagnostic tests used with this approach are not supported by a sound rationale. (...) the forward flexion tests should be used with caution as they are not likely to be good indicators of sacroiliac dysfunction. Similarly, static findings in the lumbar region should be corroborated with motion testing, altered end-feel, segmental tissue texture change and possibly pain provocation, as the Fryette predictive model does not appear to be valid in the lumbar spine." (Fryer, 2000)

Besides clinical trials palpation is a very important diagnostic tool in osteopathy.

According to D. Muzzi *"palpation as a measuring tool ..."* is *"perceived as a highly subjective method and therefore is often declared to be invalid"* (Muzzi, 2005). To make the validity of a palpatory examination of the patient more trustworthy, he recommends to compare an analyst with himself (one and the same osteopath examine before and after treatment), and also because the same person has lots of experience. Nevertheless, there remains, according to Muzzi, a bias or prejudice of the examiner, who perhaps has a personal interest in the outcome of the investigation, if the study is not fully blinded. In his article he quotes a letter from Michael Patterson as well, Associate Editor of the JAOA and professor and administrative director of the Department of "Osteopathic Principles and Practice" at the Nova Southeastern University in Florida.

> "... Too often palpation is used as a dependent, variable measuring instrument and thereby it is absolutely uncertain whether adequate blinding as well as measurement for repeated reliability is available." (Patterson, 2001, cited in (Muzzi, 2005))

3.3.1.3. Unclear definitions using the example of 'manipulation'

Manipulation (Latin) signifies in its original meaning 'handle' or 'artifice'. In manual medicine, manipulation represents a range of manual techniques that serve to resolve a blockage (Wikipedia).

Various therapeutic professions such as osteopaths, chiropractors and manual therapists, however, have a different understanding of manipulation. Even within osteopathy one distinguishes manipulation techniques with varying intensity. First of all it must be determined whether manipulation relates to a variety of manual forces used on the patient or whether the term merely refers to "High Velocity Low Amplitude Technique" (HVLAT) with or without an associated cracking sound that arises frequently when opening a joint blockage.

> "The key issue to resolve internationally and inter-professionally is this: does manipulation refer to a range of manual forces applied to the patient, or does it refer only to HVLAT technique, with or without an associated 'pop'."(...) "It is important that this process is ongoing and informed by research regarding the basic mechanisms and effects of osteopathic techniques." (Lucas and Moran, 2007a)

For standardization of studies, it is essential that manipulation of the locations (anatomically) and intensity of the applied force (physically) are precisely defined and hence it becomes clear what controls need to be done in a study.

> "If researchers cannot define the 'active ingredient' in treatment, as it is the case in both acupuncture and osteopathy, this poses a problem when deciding on active and control treatments." (Leach, 2008)

In addition, the implementation of a manipulation can proceed in extreme different manners, which depends largely on the skill and the level of training of the osteopaths (Chaitow et al., 2004). Kirk even presumes in his study published in 2005, that the outcome of the study will depend essentially on the skills of the involved osteopaths.

> "It is possible that if a further study were to utilize experienced practitioners (instead of novice practitioners working under the guidance of more experienced osteopath) then the effects of osteopathic intervention may be more evident" (Kirk et al., 2005).

3.3.1.4. Osteopathy is not a monotherapy

An osteopathic treatment usually does not just apply one specific manipulation. The use of a wide range of different osteopathic techniques is more frequent depending on the individual diagnosis.

> "Osteopathic manipulation are not single, well defined monotherapies, but rather collections of various interventions that are often tailored to the needs of individual patients and that reflect the specific practitioner's training and preference" (Cherkin et al., 2003);

> "Osteopathy as practiced is never a single 'magic bullet', it is a complex and integrated intervention compromising touch, advice and delivery of a number of manual techniques selected by the practitioner in consultation with each specific patient" (Leach, 2008),
> "In my own practice, it is my experience that most patients respond better to a multifactorial approach than to individual interventions." (Douglas Lewis. N., quoted in (Chaitow et al., 2004))

Therefore, osteopathic treatments are actually a "black box". An RCT to test a treatment consisting of several manipulations is statistically and in practice very difficult, extremely expensive, and therefore hardly feasible. The testing of the efficacy of 5 parameters, with all the controls would require 32 groups (5x5 applications and 7 controls). That is to say that an RCT of a typical osteopathic treatment does not exist yet. Therefore, osteopaths defend themselves, when the results of RCTs of a (more or less well-defined) manipulation with negative evidence are extrapolated onto effectiveness of osteopathy. This happened recently as a media-efficient study (more precisely, an overview of multiple meta-analyses) by Ernst and Canter concluded that any kind of spinal manipulation is not recommended for back pain (Ernst and Canter, 2006). Lucas comments that the relevance of osteopathy is not questioned by this publication, because spinal manipulation is not solely used during osteopathic treatments.

> "... osteopaths rarely ever use spinal manipulation in isolation and so this review {Note (Ernst and Canter, 2006)} is not representative of osteopathic treatment and therefore does not represent a challenge to the relevance of osteopathy." (Lucas and Moran, 2006)

The different understanding and consequently different application of the same technical terms is joined by the different intentions in the application of a technique on the part of the practitioner or even of the patient, who understands the effect of manipulation in his or her own manner.

> "The problem, when examined in this manner, is that spinal manipulation is used for various purposes. Satisfying a hunger for touch, the longing for attention, and the search for a reliable somatic indication of these complaints, all of these factors blur the picture of why people visit manual therapists" (John Hannon, DC, quoted in (Chaitow et al., 2004)) .

3.3.1.5. Clinical trials are often carried out without a clear distinction of osteopathy

In addition, a group of volunteers may simultaneously receive other applications besides osteopathy and thus no evidence of the effectiveness of osteopathy is possible. On the one hand this can be due to the description of the method and its supposed effect being unclear.

> "If researchers cannot define the 'active ingredient' in treatment, as it is the case in both acupuncture and osteopathy, this poses a problem when deciding on active and control treatments" (Leach, 2008).

On the other hand the ethical issue matters as well, particularly to design a good placebo treatment (for the control group) for a manual approach, without giving the impression of working solely with a placebo of attention and care. Moreover, some diseases do not allow

the mere application of a so little studied medicine such as osteopathy.

3.3.1.6. Placebo effect of osteopathy

The placebo effect has a greater or lesser degree in almost every manual treatment. This shall be eliminated (or minimized) as proof of efficacy of a specific therapy in RCTs, by involving control groups, which receive a pseudo-treatment (or pseudo-medication).

This is virtually impossible with osteopathic treatment. The placebo effect probably plays a major role as a nonspecific impact on the effectiveness of osteopathic treatment. Matthias Beck refers to osteopathy as *"caring medical attention"*, which may, through the therapeutic relationship, strengthen the enshrined archaic belief to become healthy. The latter he assigns not only as a *"phylogenetic advantage over millions of years"* but also as a *"salutogenic resource"*.

> "Modern placebo research assumes in a hypothesis that man disposes of an enshrined archaic belief to become healthy again in an event of illness. This belief has proven itself over millions of years even as a phylogenetic advantage and is our perseity of a salutogenic resource. It can be greatly strengthened by a therapeutic relationship and thus is to be considered as a basis for any caring medical service, which includes osteopathy." (Beck and Unverricht, 2005)

Lucas describes the interaction and mutual reinforcement of specific and non-specific effects of a treatment method. He is even considering integrating the placebo effect as an important part of the self-healing mechanism of human psychophysiology.

> "It is interesting to consider how the specific effects of treatment might interact with the non-specific effects of the treatment. For instance, since Licciardone et al. report OMT to be more effective than placebo in the treatment of low back pain (Meta-analysis 2005), this knowledge will increase the positive expectation of osteopaths, which may in turn increase the positive expectation of the patient. An increase in positive expectation will increase the non-specific effects, which in turn will increase the overall effectiveness of OMT. The irony is this: the more specific a treatment becomes, the more practitioners are likely to enhance, via positive expectation, the non-specific elements of a treatment. This phenomenon may explain why patients, who have received OMT in the past, may have a greater response to OMT than those who have had no prior experience with OMT, as was demonstrated in a recent study.{...}, the fact remains that these non- specific responses are an important feature of the self-regulatory mechanisms of human psychophysiology. Rather than viewing OMT as something that should be separate and distinct from non-specific placebo effects, perhaps the effectiveness of OMT depends to same extent upon an interaction between OMT and placebo responses?" (Lucas, 2005).

Prof. Saller from the University of Zurich undertakes similar considerations regarding a specific calculation of the placebo effect in the choice of treatment method.

> "The integration of subjectivity is an essential element of that wholeness that is desired. Wholeness does not mean to do as much as possible undifferentiated, but to choose and design in each case a disease-related and personal multidimensional treatment. Hence, much of what is discussed under "placebo" gains an operational and non-discriminatory approach: a focused and patient-specific mobilization of self-healing capabilities of the individual and the subject." (Saller, 2008)

3.3.1.7. Inexperience with scientific methodology

Inexperience in the selection of the measurement methods as well as the documentation and analysis of results equally plays a role. Lucas describes in his editorial about the relevance of osteopathic research the need to improve the methodological weaknesses or deficiencies in the presentation of data.

> „If the research is there, but suffers from methodological weakness (such as poor operational definitions of the manipulative protocol), or flaws in reporting the data (such as failing to report dropouts) then we must resolve to improve research protocol design and reporting in order to ensure that it is not excluded from systemic reviews." (Lucas and Moran, 2006)

He correctly asks: *"Where are the research data from the osteopathic profession that demonstrates the effectiveness of the interventions commonly administered, some of which have been in use for more than a century? If the evidence was there in a format consistent with current standards in research reporting and biomedical publishing, then the evidence would be included in systemic reviews." (Lucas and Moran, 2006)*

McGovern sees a great challenge for osteopaths without adequate education in scientific methodology to face the processing and transfer of scientific results into practice.

> "The difficulty of the transition to translational medicine {Note: the so-called translational medicine requires the physician / healer to solve disorders by working together rather than 'diagnosing' hypothetical diseases; In this context, disease is understood as a part of life and not as a state of illness, whereby the whole person and their interactions between genes, environment and lifestyle is incorporated into finding a solution.} with its view of scientific evidence lies in the fact that most therapists are not trained to apply scientific methods or to evaluate scientific studies. Despite all, they are expected to process the huge amount of results in research and to transfer them into clinical practice." (McGovern, 2006)

His final view is positive, that osteopaths remain experts in the area of personal values and life circumstances of their patients, even if they - like other interactive therapists - are not trained scientists (McGovern, 2006).

3.3.2. Inexperience in dealing with ethics committees

Another aspect is the lack of experience in dealing with ethics committees, which may potentially render the execution of a well-planned study impossible.

> "One of the major difficulties is that there aren't enough experienced and available personnel within the profession to undertake high quality effectiveness studies. (...) A decent clinical trial will require experienced and competent investigators who can prepare robust experimental designs, orchestrate grant writing to secure funding, gain ethical approvals, secure suitable clinical facilities,

> recruit, and brief practitioners, and liaise with administrators, in addition to the patients. Then of course, there is data analysis, manuscript preparation and publication.“ (Lucas and Moran, 2006)

Thus, an experienced scientist can already estimate in advance what is feasible under the local policies and concepts of ethics, or help to act convincingly and to debate. This will not likely be achieved by a student of osteopathy, who has just begun to collect experience from the recently learned in the daily practice.

3.3.3. Inexperience in collaboration

An exemplary way to compensate for the lack of cooperation with institutions such as hospitals and research institutions is distinguished by Dr. James J. McGovern, with the research project launched by him in 1998 at the Kirksville College of Osteopathic Medicine (KCOM). John Heard reports that McGovern founded a separate department at the university level in support of research programs.

> “This department organizes research grants and develops programs to assist in the preparation of research proposals.{...} Furthermore, an interdisciplinary research committee (IRC) was set up, which is composed of basic research scientists, clinical researchers, nurses and support staff, from the department. This group will set priorities for the research activities and will help individual researchers to orient their individual projects. To support the early development of these new research activities, a Strategic Research Initiative Fund has been introduced to provide the seed money for pilot projects, particularly in the field of osteopathic manual therapy. {...} In addition, an external committee of scientific advisors staffed with leading scientists from around the country, helps to set the general direction of the institute. The SRI (Still Research Institute) has become the centre of the development of clinical research at the university.” (Heard, 2006)

Sceptical and simultaneously motivating, he notes that the manual techniques are indeed only part of the many treatment forms of osteopathy, but that precisely these are most easily ‘visible’ to the general public and therefore are probably essentially responsible for their popularity within the complementary medicine, especially, *“when traditional and more expensive treatments only yield temporary relief” (Heard, 2006).*

4. Clinical trials on the effectiveness of manual therapies including osteopathy for back pain

Since, for various reasons, it is impossible to establish a general overview of the clinical trials relating to osteopathy and the question of its effectiveness within this thesis, I will narrow it down exemplifying publications with the topic of back pain in journals within the last fifteen years.

On the one hand, because back pain is among the leading reasons for a consultation and, on the other hand, because pain in the lower back area, aside of headaches of cervical origin, belongs to the two best documented pain phenomena.

> "The two best-documented exemplars for the application of structure-function approaches in diagnosis and treatment of patients with persistent pain symptoms are lower back pain (LBP) and cervicogenic headache." (Kuchera, 2005)

4.1. Introduction to the topic of back pain

A backache initially describes all the pain of varying intensity in the entire spinal area, whereby the region of the cervical or lumbar spine is most frequently affected.

Depending on the duration of back pain one distinguishes (I) acute: first-time or occurring within a day after at least a six month symptom-free time-lapse and not exceeding a continuous three month period, (II) temporarily: not exceeding a continuous three month period and not recurring within one year, (III) recurring: more than one episode and during less than half of the days of the year, or (IV) chronic: usually more than one episode on more than half of the days of the year. 90% of chronic back pain are *nonspecific*, i.e. within the scope of medical examination no triggering underlying disease can be identified, the remaining 10% are described as *specific*, because they are caused by certain diseases such as degenerative (osteochondrosis) or inflammatory (Scheuermann's disease, Bechterew's disease or ankylosing spondylitis) spinal diseases, vertebral fractures or tumors, spondylolisthesis ('slipping vertebrae', i.e. displacement of a vertebra), stenosis of the spinal canal, herniated discs or posture changes.

The causes of back pain are very diverse, the most common being a dysfunction of the joints in the region of the spine, but internistic diseases are associated with back pain as well. Ultimately, the spine plays an important role as a 'target organ' for psychosomatic problems as well.

In Germany back pain, following respiratory infections, is the second leading cause for seeing a doctor. Statistically speaking 27-40% of the people suffer from it, 70% have the pain at least once a year and 80% complain of back pain at least once in their lifetime.

Back pain among men is the most common cause with 14%, and among women with 11% the second leading cause of work absenteeism. The economic significance is even more apparent when one considers that spinal problems represent more or less the direct cause for early retirement.

The majority of those affected has a good prognosis. In more than half of all cases, the pain disappears within a week, after two weeks approximately 80% are improved to the extent that they can go about their normal activities again. However, there are frequent relapses.

The treatment depends on the cause of the complaints, often it is attempted to tackle this in advance with preventative spinal training programs and specific exercises.

Besides symptomatic therapy (injection of muscle relaxants, physical therapy, massage, etc.), especially the administration of nonsteroidal antiinflammatory drugs (NSAID) intended to prevent the formation of a pain memory proved to be effective for acute back pain. In some cases, however, surgery cannot be avoided.

Many types of applications exist for chronic pain such as acupuncture, osteopathy, manual medicine, chiropractic (spinal manipulation), traction, aids such as corsets, physical therapy, biofeedback, transcutaneous electrical stimulation, relaxation techniques such as autogenic training or progressive muscle relaxation according to Jacobsen, yoga, Alexander Technique, Feldenkrais, and cognitive behavioral therapy.

Patients experience many of the mentioned methods as soothing, but many insurances consider the cost-benefit ratio inappropriate and studies proving their benefits are scarce and of little significance, respectively.

4.2. Brief history of studies related to the spine

Until the mid-20th century, anatomic-pathological studies were still in the foreground, trying to describe the structure of the spine with increasing detail. Prof. Dr. A. Adamkievicz is worth mentioning here, who wrote several pathological studies on blood vessels of the human spinal cord during the period of 1876-1881 at the Institute of Experimental Pathology, University of Cracow.

With this, an essential basis was established for subsequent conclusions about the function of the spine in its environment: neuromuscular mechanisms and biomechanical reviews, refined by the osteopaths John M. Littlejohn, Louisa Burns, Irvin K. Korr and Harrison H. Fryette.

Not until the second half of the 20th century, were physiological studies intensified, enabling a better understanding of the pathogenesis of back pain.

The first clinical trials emerged around the end of the 20th century, being the first to carefully examine the therapeutic measures applying to back pain. The wide variety of induced methods, while health insurances simultaneously demanded a health care cost deflation, necessitated a review of each measure regarding their efficacy, versatility, safety and cost efficiency of treatment.

Soon the large number of data published demanded review articles and meta-analyses. Their results or their interpretation were evaluated very critically, resulting in a return to larger-scale studies following more clearly differentiated criteria. Moreover, one is now trying to find some indication about the cost-benefit effect of the applied therapy.

4.3. Questions and results of selected clinical trials of spinal manipulation and osteopathy for back pain

4.3.1. Review of van Tulder 1997

In 1997, Dr. Maurits W. van Tulder, a renowned epidemiologist from the Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam, The Netherlands, created a review of the conservative treatment of back pain in the lower back (LowBackPain, LBP). Evaluating many studies of different therapies, he concludes that for acute LBP only the treatment with non-steroidal anti-inflammatory or myorelaxing drugs shows an effect. In chronic LBP, manipulation as well as spinal training courses and exercises achieve a short-term effect. However, he basically criticizes the methodological approach of most studies, wherefore he could only utilize 25-28% of all RCTs on acute and chronic LBP: “The quality of the design, execution, and reporting of randomized controlled trials should be improved, to establish strong evidence for the effectiveness of the various therapeutic interventions for acute and chronic low back pain.” (van Tulder et al., 1997)

4.3.2. Review of Cherkin et al. 2003

Daniel C. Cherkin and colleagues from the Center for Health Studies, Washington University, provided a systematic overview of all syntheses and meta-analyses for the treatment of back pain through acupuncture (a total of 14 RCTs), therapeutic massage (a total of 5 RCTs) and spinal manipulation (of 52 RCTs) registered during 1995-2003 in MEDLINE, EMBASE, and Cochrane Controlled Trials. Their effectiveness, safety, and cost of treatment were compared in the article. Motivation for the study of complementary methods was provided by the fact that only a few conservative treatments demonstrated efficacy for the acute and chronic (van

Tulder et al., 1997) and dissatisfied patients often look for complementary or alternative therapies, respectively (Complementary and Alternative Medicine, CAM).

The 3 investigated therapies were all attested as highly secure.

The small number of RCTs on therapeutic massages showed a benefit, while the effectiveness of acupuncture remained questionable mainly due to the generally poor quality of the studies. In the case of spinal manipulation, the analysis of 52 RCTs showed a clinical benefit, but was not greater than the common current methods. Compared to therapeutic massage, it is worse in terms of cost and effect on persistent back pain (Cherkin et al., 2003).

The most extensive and youngest of the meta-analyses on manipulation of LBP compared by Cherkin et al. is the one by W. J.J. Assendelft, which is discussed in the following in more detail.

4.3.3. Meta-analysis of Assendelft et al. 2003

Willem J.J. Assendelft et al. compare spinal manipulative therapy with (i) placebo (sham) and other established therapies such as (ii) general medical care and analgesics, (iii) physical therapy and body workout, (iv) spinal training program, and (v) a group of ineffective interventions such as traction, corset, and bed rest - which have been summarized into a cluster for this purpose - trying to make a statement regarding their effectiveness. Looking through 1153 RCT abstracts published during 1966-2000, 53 articles were spotted from which 39 RCTs were selected for the meta-analysis by taking the inclusion criteria into account.

> "There is no evidence that spinal manipulative therapy is superior to other standard treatments for patients with acute or chronic low back pain." (Assendelft et al., 2003)

The spinal manipulation was only advantageous compared to the placebo therapy or the so-called 'ineffective' therapies, rather classified as more 'dangerous' therapies. This benefit was merely clinically significant regarding short-term pain reduction, but not statistically significant when considering all of the documented parameters.

> „The point estimate of improvement in short-term function for treatment with spinal manipulative therapy compared with the ineffective therapies was clinically significant but did not reach a conventional level of statistical significance (2.1-point differenc on the RDQ)." (Assendelft et al., 2003)

Regarding the effectiveness of osteopathy the overview by Cherkin et al. and the meta-analyses by Assendelft et al., however, reveal little, because the analyzed RCTs were dominated by chiropractic and physical therapies.

> "Spinal manipulation, performed mostly by chiropractors in the United States, is the most popular CAM therapy for back pain" (Cherkin et al., 2003).

In the following, studies dealing explicitly with osteopathic manipulation are presented.

4.3.4. RCT of Andersson et al. 1999

In 1999, the physician Gunnar B.J. Andersson and his group published in the prestigious New England Journal of Medicine (NEJOM) a trial (RCT) in which 83 patients receiving osteopathic manipulation of the spine (OMT) were compared with 72 patients receiving standard therapy. OMT consisted of a series of techniques such as *"thrust, muscle energy technique, counterstrain, or myofascial release"* (Andersson et al., 1999), while the standard therapy used NSAIDs, analgesics, active physical therapy, ultrasound, diathermy, hot or cold-packs, corset, or transcutaneous electrical stimulation.

After 8 consultations during a 12 week period patients in both groups improved regarding pain sensation, function and satisfaction according to the inquiry through the Roland-Morris-Oswestry questionnaire, a visual analog pain scale (VAS) and measurement of range of motion, as well as the straight-leg raising test. Statistically, however, the difference was not significant.

> "The osteopathic treatment group received less medication and less physical therapy than the standard-care group, and the difference in cost were significant." (Andersson et al., 1999)

Although the cost factor was not specifically an issue of the planned investigation, Andersson et al. conclusively establish that the osteopathic treatment deserves an investigation based on a formal cost-benefit analysis.

> "... because of the study design, we could not determine differences in cost between the treatment groups", {…} "this type of treatment (note: OMT) deserves careful examination through a formal cost-benefit analysis. " (Andersson et al., 1999)

In the introduction, the term 'manipulation' is given quite some attention, and differences between the chiropractic and osteopathic approach are highlighted. The difficulty of developing a placebo treatment for the manipulation is pointed out as well.

> "It is difficult to develop a placebo for manipulation. {…} We decided against using a placebo or non-treatment group because it is not possible to prevent patients with back pain from initiating self-care (by adjustment of activity and use of pain medication). " (Andersson et al., 1999)

To minimize the placebo effect, which possibly results from the amount of visits to the osteopath, the patients in the standard therapy group were summoned equal amount of times.

> "The frequency of patient visits is typically greater when patients are undergoing manual therapy than when they are receiving standard allopathic care. We were concerned that the greater frequency of visits would introduce a placebo effect by itself in the osteopathic-treatment group; we therefore

> provided the same number of visits (eight) for both groups, on the basis of information from the osteopathic physician." (Andersson et al., 1999)

The quality of the study was mainly suffering from the underpowered number of patients.

> "The main areas of methodological weakness in our study, according to the criteria of Koes et al., were the size of the study group (72 in the smaller group, as compared with the ideal size of more than 100), the presence of other interventions, the lack of a placebo control group, and the lack of blinding of the patients." (Andersson et al., 1999)

Another problem arises from the fact that a variety of methods were approved within the two reference groups. Furthermore, no distinction was made between acute and chronic LBP.

4.3.5. Meta-analysis of Licciardone et al. 2005

Licciardone et al. published a high quality meta-analysis in 2005, in which OMT was explicitly compared to the different control therapies for LBP. Six out of 389 studies published during 1973 - 2001 in the U.S. or UK and meeting the inclusion criteria of the meta-analysis were selected for this purpose. Two of these compare OMT with two other methods, the others in each case are compared with another one (placebo manipulation, massage, standard therapy, chemonucleolysis, short-wave diathermy). Hence, 525 patients with various types of LBP (acute, chronic, pain of varying duration, once with radiation into the leg, once with menopausal symptoms) were taken into account in the evaluation.

Here, solely the efficacy was assessed by the scale of pain sensation, because other factors were not considered in all the studies.

> "This study focused only the efficacy of OMT with respect to pain outcomes, because data concerning other factors (Generic health status, back specific function, work disability, and back-specific patient satisfaction) were not consistently reported in the included trials." (Licciardone et al., 2005)

The sensation of pain was mostly registered by blinded patients using pain scales, each, however, in inconsistent intervals (1 week to 12 months) of the intervention.

In 4 out of 6 studies, OMT was used in the sense of osteopathy as a *"Variety of techniques, individualized to patient"*, in the other two a range of osteopathic techniques was applied.

In summary, it was established that OMT can significantly improve LBP, which was not solely due to placebo effects, as pain improvement was indicated as low in the case of placebo treatment. This improvement in pain lasts for at least 3 months.

> "OMT significantly reduces low back pain. The level of pain reduction is greater than expected from placebo effects alone and persists for at least three months." (Licciardone et al., 2005)

Nicholas Lucas comments hereto in an editorial that *"Even if a treatment is shown to be more effective than a placebo, it does not follow that the entire response can be attributed to specific effects of the treatment."* (Lucas, 2005)

According to him, the psychological aspects of the mechanism of the placebo effect seem to play an essential role thereby, given the positive expectation and Pavlovian conditioning as nonspecific effects for self-regulatory mechanism and hence for the overall effect of the OMT and therefore definitely takes this into consideration.

> "We can therefore consider the likelihood that effectiveness of a treatment is a combination of both specific and non-specific mechanisms, and rather than trying to enhance only the specific mechanisms, we should consider how we might purposely enhance the non-specific mechanisms." (Lucas, 2005)

Licciardone et al. require further studies on long-term effects of OMT and to investigate the cost-benefit effectiveness.

> "Additional research is warranted to elucidate mechanistically how OMT exerts its effects, to determine if OMT benefits are long lasting, and to assess the cost-effectiveness of OMT as a complementary treatment for low back pain." (Licciardone et al., 2005)

The authors noted that previous RCTs were insufficient regarding the number of subjects, variations in methodology and analysis, and the fact that the treatment took place in an outpatient practice.

> "Several randomized clinical trials of OMT for low back pain have been conducted. These all involved subjects in ambulatory settings; however, they included relatively small numbers of subjects and were characterized by variations in methodology and outcomes among trials." (Licciardone et al., 2008)

4.3.6. Study Protocol of Licciardone et al. 2008

As a result of these findings Licciardone et al. are developing the following outline for a clinical trial using the model of an RCT, in which the osteopathic treatment (OMT) and ultrasound physical therapy (UPT) shall be compared to each other and to the corresponding placebo treatments (Licciardone et al., 2008).

For this purpose, patients with constant or intermittent back pain are recruited for at least 3 months via advertisement in local newspapers and doctors' offices during the period of August 2006 to June 2010. The selection of subjects according to the inclusion or exclusion criteria, respectively, shall be made by telephone and subsequently by clinical selection process. The volunteers will be compensated for time and travel for each study-related visit. 488 volunteers will be divided by randomization into four equal sized groups of 122 subjects: Group A will receive active OMT and active UPT, group B will receive placebo-OMT and active UPT, group C will receive active OMT and placebo-UPT and Group D will receive placebo-OMT and placebo-UPT.

To clarify the concept of OMT, he initially cites the 4 principles of osteopathy and chooses to use the open form of treatment in his study allowing a dynamic physician-patient interaction.

> "OMT techniques should be individualized to the patient, and may need to be refined or changed over time based on the patient's response to OMT. {…} Ideally, practitioners should address how structure

> and function may affect low back pain and its progression, and then provide OMT by combining the most appropriate techniques from among the many available options." (Licciardone et al., 2008)

For general guidance it is mentioned to use techniques according to the glossary of osteopathic terminology. This seems all the more important than the treatment providers are coming from the following group: Specialists (including affiliated practicing physicians), residents or predoctoral fellows within the Department of Osteopathic Manipulative Medicine of the Texas College of Osteopathic Medicine at the University of North Texas Health Science Center. For a detailed examination of patients, the approach of the 'dirty dozen' framework program is proposed, which refers to the six most common dysfunctions found in patients with back problems. The ultrasound treatment is carried out by the same practitioner conducting OMT and will require approximately 10 minutes of the one-hour treatment, which shall be held at an interval of 1-2-4-6 and 8 weeks following randomization. Following each treatment, a pain assessment is also done by the patient according to a visual analog pain scale (VAS). In addition, at an interval of 4-8 and 12 weeks after randomization, an evaluation of other parameters such as specific functions of the spine, general health and work ability, as well as patient satisfaction by means of various questionnaires, is done. Concomitant diseases and concomitant therapies shall be documented in this additional evaluation as well.

> "Additional data relevant to back pain, medical co-morbidities, and other co-treatments will also be collected." (Licciardone et al., 2008)

Thus, the research group does not exclude for instance the usual treatment by service providers in patient care: *"Subjects will be allowed to receive usual care from their personal health care providers."* (Licciardone et al., 2008)

The placebo-OMT is composed of a kind of *"hands-on contact"* in various positions, which is also used in the active OMT. The placebo-UPT consists of an application of the ultrasonic head to the affected area, but the ultrasound frequency lies below one with a therapeutic effect.

Based on this protocol, it obviously may measure up to the criticism of a small number of patients, but the fact that osteopathy alone is only applied in one of the four groups, and here in the open form administered by various 'experts', shows how complex the evaluation of the results will be.

Even if the clinical results could still be unique, a statistical analysis is burdened with many variables and is therefore expected to be rather vague or even distorted.

4.3.7. Pragmatic Trial of the UK BEAM Trial Team 2004

In a randomized pragmatic trial on spinal manipulation by osteopathy, a group of scientists in the UK tried to find out more about the significance of manipulation and/or exercise programs for the treatment of patients with *"simple low back pain"* (Team, 2004b). For this purpose, 1334 patients with low back pain, distributed from 181 general medical practices over the entire United Kingdom (UK), were documented during the period from March 1998 until April 2001. Questionnaires were used by the patients to describe their health and therefore a selection for the study could be made. Further surveys were made before randomization and at intervals of 3 and 12 months of randomization using the Roland-Morris questionnaire (back-specific functions in everyday life) and a modified Von-Korff-score (low back pain and functional efficiency) as well as other questionnaires on general health status, back pain, dealing with the back pain and fear avoidance beliefs as well as physical and mental well-being (SF-36): *"participants completed questionnaires on general health, back pain, beliefs, and psychological wellbeing"* (Team, 2004b).

The groups received a 'Basic Minimum Treatment', meaning: education on dealing with acute back pain according to generally known guidelines (e.g. continuation of normal activity and avoidance of rest), introduction by specially trained personnel to the 'active management' of back pain and an information brochure entitled 'The Back Book'.

Afterwards, on 8 separate days, one group received a 60 minute tutorial according to the exercise program 'back to fitness' by a trained physiotherapist. The courses took place over a period of 4-8 weeks with a refresher after 12 weeks.

Another group received a package of manipulation techniques as recommended by chiropractors, osteopaths and physiotherapists in the UK. The 8 treatments were held in private practices over a period of 12 weeks, each treatment lasting about 20 minutes. Practitioners were skilled manipulators of the above-mentioned professions and confirmed that a HVLAT technique was applied at least once on most of the patients: *"They agreed to do high velocity thrusts on most patients at least once."* (Team, 2004b)

A third group received a combination of manipulations and exercise treatment program, whereby a 6-week period with eight manipulations was followed by a 6-week phase of exercises consisting of 8 hours of guided training and including a refresher after 12 weeks as well.

Results: All groups improved over time. The exercise program alone improved the back function of patients after 3 months with little significance, while after one year no beneficial effect was detected anymore. The groups receiving manipulative or combined treatments, the

function of the back significantly improved up to one year (regardless of the application site), although the effect was rather low and decreased over time.
But the question remained open whether the benefits are limited to treatment in relation to their costs: *"The large cost of back pain means that small differences in clinical outcomes may have large economic effects."* (Team, 2004b)
The results regarding this question was published in an accompanying study in the same journal (see in 4.4.1).

4.4. Studies on the economic aspect of treatment of back pain

4.4.1. Cost-utility analysis in a pragmatic RCT of the UK BEAM Trial Team 2004

In an extension of the above-mentioned study, a cost-utility analysis was performed (Team, 2004a). To this end, 1287 (96%) of the participating patients received a questionnaire (i.e. EQ-5D) to assess health parameters such as mobility, independence, daily activities, limitation by pain and psychological state at three different time points of the study (at baseline, and 2 and 6 months after completion of treatment). (Note: EQ-5D is a standardized instrument utilized as a measure of health outcome; for detailed information see: www.euroqol.org.) The scores were used to calculate the quality adjusted life year (QALYs) of the patients in the study. (Note: QALY is a measure for the health status corresponding to life quality in one year of life. A QALY of 1 indicates one year without any disease burden, whereas a QALY of 0 indicates death).

The economic evaluation under consideration of QALYs showed that recommendations for treatment strategies from decision makers depend on the accepted cost ceiling. Much below 3800£ "best care" in a general praxis has been most effective. Between 3800-8700£, a combination treatment (spinal manipulation followed by exercise) showed the greatest cost-utility. Interestingly, beyond 8700£ spinal manipulation alone was better than the combination therapy and was good value for money.

4.4.2. Pragmatic RCT of Williams et al. 2003

In a pragmatic RCT, 201 patients with back problems (upper, middle and predominantly lower back) persisting two to twelve weeks, were documented. They provided information on

the quality of pain on a specific pain scale (Extended Abeerdeen Spine Pain Scale, EASPS) and moreover, secondary parameters were gathered such as restriction in daily life, health, quality of pain and dealing with the pain, by various questionnaires (SF-12, EuroQol and Short-form McGill Pain Questionnaire). The survey was conducted at three time points: at the beginning of the study, after two and again after six months.

Additionally, the costs were estimated based on the physicians' records involved in the six-month period before and after randomization. In doing so, it was attempted to capture the overall costs and in parallel the costs emerging in connection with the back problem. The statistical analysis according to the 'bootstrap-analysis' made it possible to exclude outlier data (a few patients, demanding an extremely large amount of services).

After randomization the group sizes were already unequal, supposedly being negligible for the significance of the study.

> "There was an imbalance of 19 between the number of subjects in the control and treatment groups. {…} The imbalance was not large enough to affect the power of the trial." (Williams et al., 2003)

Therefore, the control group received standard care, the osteopathy group an additional treatment package, which included osteopathy as well.

> "The treatment package consisted mainly of osteopathic spinal manipulation, but also advice about keeping active, exercising regularly and avoiding excessive rest. Occasionally, if symptoms persisted despite osteopathy, tender ligaments or peripheral joints were injected with corticosteroid and local anaesthetic." (Williams et al., 2003)

The results in terms of improving symptoms in patients with subacute low back pain, was more distinct in the osteopathic than in the standard treatment group.

> "Patients presenting to their GP with subacute spinal pain reported greater improvement in short-term physical and longer-term psychological outcomes if treated in a primary care-based osteopathy clinic in addition to usual GP care" (Williams et al., 2003)

After two months, the improvement was significantly higher in the osteopathy group for the EASPS and the SF-12, i.e. the pain assessment and the assessment of mental state. After six months, the difference was only statistically significant with respect to the SF-12, because apparently the control group continued to improve, while the osteopathy group continued to shrink due to unreturned questionnaires. In conclusion, the authors advise against a generalization of the result, given that the conditions at the clinic, where investigations took place, were classified as being exceptional. Instead they recommend repeating the study in different locations.

The difference in the outcome parameters simply enabled a cost-consequences analysis. A cost-benefit analysis as well as a cost-effectiveness analysis, however, must remain subject of a subsequent publication.

> "Given the variety of different outcome measures employed, we used cost-consequence analysis, and estimated all the identifiable incremental costs and consequences (health outcomes) without aggregation. Cost-effectiveness and cost-utility analysis will be the subject of a subsequent publication." (Williams et al., 2003)

4.4.3. Cost-utility analysis of Williams et al. 2004

Subsequently, a cost-utility analysis was compiled by the research team at the same clinic (Williams et al., 2004). Therefore, 200 patients with back problems (upper, middle and lower back) persisting between two and twelve weeks, were randomized and assigned to two equally sized groups (OMT and standard treatment by general practitioners vs. standard treatment on its own) during the same period (September 1997-March 2001) at the same osteopathic clinic in North West Wales allocating patients from 14 surrounding general practices.

The treatment of all patients included the standard treatment by their general practitioner. While the control group did not indulge in any further treatment, the osteopathy group received an additional 3-4 treatments by a general practitioner registered as an osteopath in a modern osteopathic clinic in North West Wales.

The questionnaires submitted by mail also included the patients' information on EQ-5D, which in their completeness were necessary for the calculation of QUALYs. The questionnaires were collected at the beginning of the study, two months afterwards (on completion of the intervention phase), and once again after six months. The results of the questionnaires were evaluated by two people not involved in the treatment and analyzed by one person involved and two people not involved in the treatment.

Data on costs were collected from the practice records for 6 months preceding and the 6 months during the trial. Herein, costs were gathered from the initial consultation as well as from investigations, prescriptions and other consultations and hospital stays (not just for the treatment of back problems!).

> "Investigations, prescribing and out-patient consultations, and hospital stays for back pain and all other reasons. Unit costs were obtained from national sources and finance officers of local provider units for the year 1999/2000." (Williams et al., 2004)

In addition it is noted that these statements of cost might be incomplete, as not all medical care occurring outside of the clinic was included, which would have led - for both groups, though - to an underestimation of the costs.

After all, the results of only 136 patients, belonging in equal amounts to the standard or osteopathic group, respectively, could be evaluated, which is considered inadequate.

> "The sample size was calculated in terms of the primary outcome measure, and the study was relatively underpowered to evaluate health utilities and costs." (Williams et al., 2004)

Thus, the osteopathy group was indeed more effective, but also more expensive than the group with pure standard treatment. In a more sophisticated analysis, which considered solely the costs related to back problems, lower costs per QALY ratio are yielded.

> "Osteopathy plus usual GP care was more effective but resulted in more health care costs than usual GP care alone. {…} Sensitivity analysis examining spine-related costs alone and total costs excluding outliers resulted in lower cost per QALY ratios." (Williams et al., 2004)

Whereby outliers seemed to appear unequally in the two groups and probably were, especially in terms of hospital costs, a major cost factor.

A generalization of the results found is considered to be problematic, because only one physician of a specific clinic conducted the osteopathic treatment. For future trials it is recommended to involve a number of osteopaths of various practices in the study. Thus is the conclusion.

> "A primary care osteopathic clinic may be a cost-effective addition to usual care, but the conclusion was subject to considerable random error." (Williams et al., 2004)

With regard to the calculation of cost per QALY ratios, one hopes for a more apparent, more standardized and more transparently outlined approach.

> "The steps for calculation of cost per QALY ratios alongside RCTs need to be clarified, standardized and made more transparent" (Williams et al., 2004)

The final cost-benefit analysis should include both statistical uncertainties as well as a more sophisticated analysis. An assessment of the distribution according to a purely punctuate distribution in 4 quadrants of different significance could be misleading, especially, if negative ratios were evaluated as well.

> "Conclusions from cost-utility analyses need to include estimates of statistical uncertainty as well as sensitivity analyses, as isolated point estimates of cost/QALY ratios can be misleading." (Williams et al., 2004)

4.4.4. Retrospective study of Crow et Willis 2009

A large-scale retrospective study at a hospital in Orlando (USA) is devoted to the economic aspect, reviewing the treatment of a total of 1556 patients with acute LBP (OMT versus standard therapy) during the period from early 2002 to end of 2005 (Crow and Willis, 2009). In this study data was subsequently collected from hospital billings, performing a comparison of total costs for health care of the OMT group with the standard therapy group. Hence, an average value for each patient per group was calculated. By comparison, the cost of patients treated by osteopathy is lower, primarily because fewer examinations had to be done.

> "OMT patients had 18.5% fewer prescriptions written, 74.2% fewer radiographs, 76.9% fewer referrals, and 90% fewer magnetic resonance imaging scans. In the OMT group, total average costs were $38.26 lower (average P = .02), and average prescription costs were $19.53 lower (P<.001). Patients in the OMT group also had $63.81 less average radiology costs (P<.0001)." (Crow and Willis, 2009)

The preliminary result therefore concludes that osteopathy could help to reduce costs in the treatment of LBP, and should encourage confirming the profitable use of osteopathy in LBP with prospective studies.

5. Discussion

Osteopathy with its integrative approach (body-mind-spirit-unit) could well meet the requirements of a multifactorial event such as back pain. The medicine developed from its philosophy has designed an approach of osteopathic manipulative treatment (OMT). Based on the results found in the examination (anamnesis and physical examination), a variety of methods have been applied aiming to restore balance (homeostasis) in neuroendocrine, respiratory-circulatory, and postural psychosympathetic terms. It knows several techniques that open the fascial pathways (metabolic pathways), maximize breathing (primary and secondary), improve the venous-lymphatic drainage and thereby restore the original cellular function (metabolism). But it also identifies measures to be taken in order to achieve different interactions with the environment (if the pain generator is expected to be found there): behavioral changes regarding exercise, nutrition and drug use, stress management, psychological support, ergonomic consulting, etc. (Kuchera, 2005).

The osteopath assesses during the overall treatment of an individual which dysfunction is to be supported by manipulation to approximate its original function again. While a chiropractic manipulation is limited to the establishment of motion in the area of the spinal joints and usually applies short, fast movements (High Velocity Low Amplitude Thrust, HVLAT), an osteopathic manipulation contains also more gentle techniques (mobilization, Muscle Energy Technique, Strain-Counterstrain-Technique, Balanced Ligamentous Tension Technique, Balanced Membranous Tension Technique, Facilitated Positional Release, Visceral and Cranial Release Techniques) aimed at changing the situation in the connective tissue to the effect that the metabolism works better and the tissue is thus assisted in its regeneration.

The dissatisfaction with ineffective, incomplete or impersonal conventional methods drives the patient with back pain to search for alternative treatments. Indeed, many of these exist. The repeatedly asked question by patients, practitioners and health insurancies is, however, which of them is really effective? Therefore, many clinical trials were done in this area on spinal manipulation, including osteopathy. The following conclusions were found in the studies presented.

On inspecting a review of moderate-quality trials (RCTs) in 1997, van Tulder et al. only found drug therapy recommended for acute back pain, spinal manipulation as well as massage or spinal training courses merely offer short-term effect for chronic back pain.

In 2003, Cherkin et al. summarize in their review that the benefits of spinal manipulation are indeed better than no treatment at all, but are not necessarily beneficial compared to other standard treatments (back schools, physiotherapy, analgesics). In the case of persistent back pain, massage can even gain advantage regarding the effect and costs compared with spinal manipulation. If it were up to this study, it would be advised against acupuncture with regard to these symptoms, as it showed no benefit.

Assendelft and colleagues came to a similar conclusion as well, finding a similar benefit of spinal manipulation and standard therapies, but which appear advantageous compared to placebo effects and methods known to be ineffective (such as corsets). But even for this difference there was no clear significance due to some shortcomings in the study.

As mentioned, these studies refer to spinal manipulation in general. What exactly is understood of it (definition of spinal manipulation), or how the intervention will take shape, only finds marginal attention, although it is sometimes pointed out that the type of manipulation can look very different depending on who it is executed: by a chiropractor , a physician of manual medicine, or an osteopath.

A study by Andersson and co-workers as well as a meta-analysis conducted by Licciardone are specifically dedicated to the benefit of osteopathic manipulative treatment (OMT). It should be noted that OMT itself only represents a part of Osteopathic Medicine, which is furthermore interpreted very differently.

In a study published 1999, Andersson et al. succeeded to understand OMT as an approach with a variety of techniques that distinguishes from the chiropractic manipulation. The authors, however, remain vague in this matter. They compared groups of patients receiving either OMT or standard allopathic treatment (i.e. mainly drugs) and found that both groups improved during the observation period with no statistically significant difference.

The meta-analysis published in 2005 by Licciardone et al. was the first to show a slightly significant improvement in low back pain with OMT, lasting at least 3 months. In his opinion more studies with larger patient numbers would be desirable including the long-term effect of osteopathy and a cost-benefit analysis as well. Such additional cost-benefit analysis is expected to generate more distinct differences than other methods. Even Andersson had already observed in his study that the osteopathy group required less additional medication and less physical therapy, although a cost-benefit analysis was not included a priori in his study design.

In 2004 Williams et al published the result of a pragmatic clinical trial known as the randomized osteopathic manipulation study (ROMANS), wherein a reduction of back pain was assessed as well (on a defined pain scale), when OMT was carried out in addition to standard treatment. Although the treatment was more expensive in absolute terms, they came to the conclusion that the cost-benefit effect (cost effectiveness) is advantageous. This study, however, had some intrinsic shortcomings. For example, all patients in the osteopathic treatment group received treatment at the same location by the same person, who was simultaneously the head of the study, while the control groups were treated by different general practitioners. Thus, the authors concede in the discussion of the article that it is quite possible that different psychological factors (i.e. the placebo effect) could have influenced the results of the two groups.

All in all one can say that the studies did not really provide convincing results that spinal manipulation or osteopathy are beneficial in the treatment of back pain, at least not compared to other standard methods. This result in turn may not be surprising, considering the large heterogeneity of the studies' in- and exclusion criteria of the subjects (age, quality of pain, comorbidities, etc.), number of treatments, presence of control groups, and selection of the outcome parameter. Even if a significant difference was found between intervention and control group, the question remains whether this occurred through a specific effect of spinal manipulation or osteopathy.

To this end a little anecdote. In football, as in other sports, it is common for club managers to replace the coach after a bad series with many defeats. It is well known that as a result the chances of the team's success increase significantly in the next 2-3 games. Thus, exchange of the coach has a statistically significant "therapeutic" benefit. However, one would be a fool to assume that the revived success of the team was specifically caused by the new coach in person or his training or tactics,

It should be noted that the benefits of spinal manipulation and/or osteopathy in regards to back pain were only a short-term effect (2-3 months), while at 6 months or longer no significant difference was demonstrated between intervention and control groups.
The discussed studies on the benefits of osteopathic or other manual intervention for back pain clearly show the difficulties of osteopathy for EbM, which I mentioned the general reason for above (in section 3.3.). Osteopathic studies have a low level of evidence, because

systematic weaknesses in the methodology exist. Clinical studies are mostly carried out without a clear distinction of osteopathy. The patients receiving osteopathic treatment for their backs usually received a standard treatment as well, its benefits already being established (painkillers, nonsteroidal antiinflammatory drugs), and which ethically could not be withheld from the patient. One of the greatest obstacles of reliable studies with hard evidence grade is that osteopathy is not a monotherapy and several manipulations are usually applied simultaneously, which in addition are vaguely defined and therefore correspond to a black box. Hence, it inevitably results in at least 3 other problems: (i) a generally insufficient number of control groups with ill-defined control treatments, (ii) the maximization of placebo effects, and (iii) the non-comparability of various studies. When individual studies are too heterogeneous, even meta-analysis of such studies become irrelevant. In that case the principle of "garbage in - garbage out" applies.

On the other hand, back pain as many other musculoskeletal complaints belong to the complex bio-psycho-social phenomena requiring a multifaceted research approach. The large number of variables for back pain and such complex methods such as osteopathy represent an almost adamant obstacle in the creation of standard RCTs, where the effect of a technique is compared to the effect of others.

Janine Leach calls for a more refined understanding of scientific evidence for proof of efficacy of osteopathy, which ascribes more importance to clinical observation, case studies and the patient's perspective (Leach, 2008). Observational studies such as cohort study, case-control study, and the case reports and/or case series can be used to formulate hypotheses and define parameters that should be measured in an RCT.

Perhaps an entirely new direction must be taken to enable the "subjectivity of the patient amidst the objectivity of the data". Prof. Saller from the University of Zurich deems it necessary to define a new plasticity of the term "evidence" (Saller, 2008). Current scientific concepts are by all means completely overwhelmed by it.

The necessity of basic research in osteopathy

In recent years, osteopaths of many countries have undergone many attempts to provide evidence from clinical trials for clinical benefits of osteopathic treatment. In my thesis, I focused on studies regarding the benefits of osteopathy and/or spinal manipulation against back pain, because the largest number of publications in recognized clinical journals exists in

this area. As mentioned above, no solid evidence has been found that osteopathy or spinal manipulation represents a beneficial effect of specific treatment for back pain. The result may perhaps not be surprising considering the complexity of symptoms and their causes. More important, and also disappointing at the same time, however, is the insight gained that osteopathy will hardly succeed to provide solid evidence for its specific benefits of any kind of therapy using RCT. In fact, such evidence has not yet been brought forth for many therapies of conventional medicine and is probably difficult to provide for any kind of manual intervention in particular. The placebo effect is too large and too difficult to be eliminated. In addition, all abovementioned barriers make it difficult for osteopathy to carry on EbM, at least in regard to the current state of osteopathic research. But in order to rise above this state, an increased interdisciplinary basic research is necessary.

The insignificance of osteopathic research is clarified when searching through the "Web of Science" for osteopathic journals. No more than one osteopathic journal can be found, the "International Journal of Osteopathic Medicine".

Only approved medical journals are found in the "Web of Science". The "Web of Science" also known as the "Web of Knowledge" (Wikipedia) of the Institute of Scientific Information (ISI) (now called Thomsen Reuter) is the largest and best scientific database consisting of more than 700 million publications of 23,000 journals and books from 256 scientific disciplines, including natural, social and arts sciences. The "Web of Knowledge" covers 11,000 webpages, including PubMed, a digital archive of the U.S. National Institute of Health, containing itself a total of 19 million references of articles from the biomedical sciences.

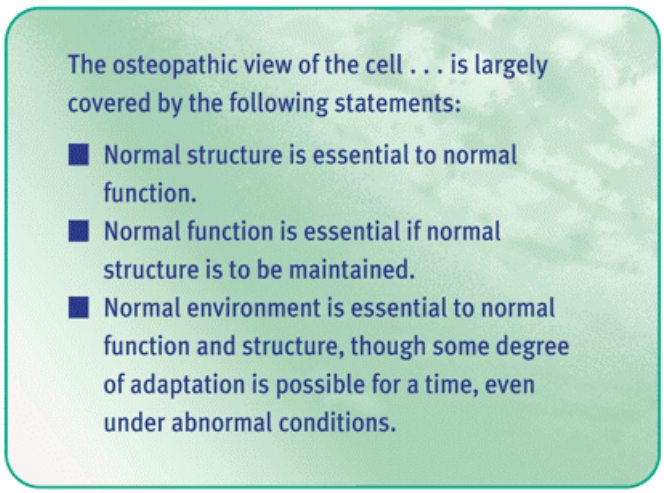
Employees of the publisher Thomsen Reuters judge according to several criteria of excellence whether a scientific journal is accepted in the "Web of Science". The evaluation is based on various factors, most notably on the frequency of citations of the manuscripts, the internationality of the authors as well as on the editorial of a journal. A rationale for the standard of a scientific journal is based on who examines the publication on their relevance and quality. If this is done by academic colleagues, who are experts in the relevant field, one speaks of 'peer-reviewed' articles.

The ISI index is nowadays the most important tool to measure the quality of publications, researchers and scientific journals and to set up a world-ranking list. Up to date, only 2 publications on studies about the benefits of osteopathic treatment (for any indication) are listed in the "Web of Science", which have attracted scientific attention to some extent based on number of citations. These are the studies discussed above by Andersson et al. and

Licciardone et al. published in the New England Journal of Medicine (with 68 citations since 1999) and in Spine (with 27 citations since 2003), respectively, on osteopathic treatment against back pain.
This illustrates that the osteopathic research is still in its infancy, let alone modern basic research on the physiology of osteopathy.

This was not always the case. Some famous pupils and successors of Andrew Still were excellent and well-known researchers. **John M. Littlejohn** (1865-1947), lecturer at the osteopathic school in Kirksville, was known for his interest in physiology. After professional differences with Still, he moved to Europe where he developed an entire philosophy based on physiological observations of the effects of movement restrictions on the physiology and the homoeostasis. His method became a milestone in the osteopathic practice, which is now mainly found in Europe (foundation of the BSO in London, legacy in Maidstone College of Osteopathy) (Stone, 1999) (p.127). In the beginning of the 20th Century, **Louisa Burns** (1870-1958) published many scientific articles on the foundations of osteopathy (Burns, 1907) (Burns, 1911b) (Burns, 1911c) (Burns, 1911a). Later she studied the effects of the restricted spinal segment on the paravertebral tissues and the components of the spinal joints (Stone, 1999) (p.77). And **Irvin K. Korr** (1909-2004) brought his entire work as a neurophysiologist (as of ca.1940) into the service of osteopathy. He coined the term of somatic dysfunction, developed the concept of the facilitated segment, and thus explored important fundamental terms of osteopathic manipulation, which were summarized in 1979 for the first time in his "Collected Works of I.K. Korr" by the American Academy of Osteopathy (Stone, 1999) (p.75-76).

Figure 2:
In 1992, the A.T. Still Research Institute published the view of the cell among other things in the textbook about the principles of osteopathy (Hulett, 1922). Taken from (Rogers, 2005).



Today, every cell or molecular biologist will agree that the structure and function of a cell are interdependent and both are in turn influenced by the environment. They have explored numerous mechanisms on how structure and function interact, and can describe them in some molecular detail. Function and dysfunction of a biological system (such as cells, organs and whole organisms - such as humans) are nowadays described in biology through the interaction of all the biochemical components of the system. This is the sum and distribution of all proteins, lipids, and carbohydrates at a given time. These are ultimately controlled by the activity of genes, which in turn are regulated by the environment (of the cell, the organ, and organism). This new research field is known as systems biology.

The "personalized medicine" has originated from molecular biology and systems biology. Initially, the pharmaceutical research has caught on to this idea in hopes of being able to administer individually tailored drugs for certain diseases through the knowledge of the genetic constitution (the genome) of each person. The reason behind this is that so far a more or less large group of patients with a diagnosed disease does not respond to a particular drug, due to differences in the genetic makeup.

How can personalized medicine be transferred onto osteopathy or in general onto complementary medicine? People are individuals and respond differently to a treatment and a particular therapist. This individual component makes it nearly impossible to reveal the effectiveness in a clinical study. In any case, the study would require a very large number of patients to demonstrate a significant effect.

Today it is possible to measure and quantify little molecular changes in a biological system (for instance in a cell, an organ, or even in a whole organism) by the modern and highly sensitive methods of molecular and systems biology. Whether this change is a genetically programmed change, such as developmental processes (e.g. embryogenesis, aging), or due to dysregulation a disease. Thus, the biological effects of any therapy can also be better understood. Personalized medicine is an important extent to EbM, because it can determine quantitatively the effectiveness in the individual. For example, we now know of genes that are solely induced by a certain mechanical pressure on cells. The quantitative measurement of such genes after a complying osteopathic treatment would be a robust specific reporter of the effect of the intervention.

New imaging technologies including functional magnetic resonance imaging (fMRI) measuring brain activity, or flow cytometry for accurate characterization of 10,000 cells per second, as well as molecular and biochemical methods (such as transcriptomics and

proteomics) for the detection of dynamic processes and all system components (such as RNA, proteins) in cell, organ, and organism, are available nowadays in basic research.
What is needed is an interdisciplinary collaboration between osteopaths with cell and molecular biologists, and life scientists.

Science can help to generate new knowledge by induction, which in turn can then be taken into consideration by deduction in everyday practice. While science is not suitable to deliver judgment on the patient's, practitioner's or the community's values, its knowledge of physiology, biomechanics, pathology, psychology of the development of measurement tools is necessary to improve the evaluation process in clinical daily routine, at least according to Prof. Stephen Tyreman passing a comment on an article with the question whether there is a place for science in the definition of osteopathy.

> "Values and their appropriate application cannot be assessed by science ... science is not the best method for assessing praxis. Science contributes to the evaluation of praxis by bringing knowledge from physiology, biomechanics, pathology, psychology and so on, as well as providing a measuring tool. However, it is important that the science is a good science, i.e. robust and open to scrutiny, whereas how the knowledge is used to achieve the best outcome for a patient requires a different kind of decision" (Tyreman, 2008).

This is a clear plea for more and better basic research as a basis for expansion of knowledge required by clinical daily routine.

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7. Annex

7.1. Abbreviations

CAM	*Complementary and Alternative Methods*
EbM	*Evidence based Medicine*
GRADE	*Grading of Recommendations, Assessment, Development and Evaluation*
HVLAT	*High Velocity Low Amplitude Thrust*
IRC	*Interdisciplinary Research Center*
KCOM	*Kirksville College of Osteopathic Medicine*
LBP	*Low Back Pain*
NSAID	*Non Steroidal Anti Inflammatory Drugs*
OMM	*Osteopathic Manipulative Medicine*
OMT	*Osteopathic ManipulativeTherapy*
PH.D.	*Philosophical Doctor*
RCT	*Randomized Controlled Trial*
RMDQ	*Roland Morris Disability Questionnaire*
UPT	*Ultrasound Physical Therapy*
UK	*United Kingdom*
UK BEAM	*United Kingdom Back Pain Exercise and Manipulation*
USA	*United States of America*
VAS	*Visual Analogue Scale*
VbM	*Value based Medicine*
WHO	*World Health Organization*

7.2. Glossary

Cochrane Collaboration

The Cochrane Collaboration is a worldwide net of scientists and clinicians with the aim of the creation, updating and dissemination of systematic reviews for the evaluation of medical therapies.(http://de.wikipedia.org/wiki/Cochrane_Collaboration,Dez 2009)

Dysfunction (somatic)

*Is an impaired or altered function of related components of the musculoskeletal system including skeletal, extra cellular matrix, related vascular, lymphatic, and neural elements." The diagnosis of somatic dysfunction is supported by visual and palpable findings of **T**issue texture changes, **A**symmetry of structure, **R**estriction of motion and **T**enderness to palpation (TART). (Glossary of Osteopathic Terminology , AAOM, 2002)*

Manipulation

(Latin for a hands-on physical intervention) is a type of passive movement of a skeletal joint with the aim of achieving a therapeutic effect by applying manual force on it. In

manual or manipulative therapy this includes a variety of techniques to release the blockage of joints or congestion in the tissues.
(http://de.wikipedia.org/wiki/Manipulation, Dez 2009)

Osteopath

"1. A person who has achieved the nationally recognized academic and professional standards within her or his country to independently practice diagnosis and treatment based upon the principles of osteopathic philosophy. Individual countries establish the national academic and professional standards for osteopaths practicing within their countries (International usage).
2. Considered by the American Osteopathic Association to be an archaic term when applied to graduates of U.S. schools." (Glossary of Osteopathic Terminology , AAOM, 2006)

Osteopathy

"A complete system of medical care with a philosophy that combines the needs of the patient with current practice of medicine, surgery and obstetrics. Emphasizes the interrelationship between structure and function, and has an appreciation of the body's ability to heal itself." (Glossary of Osteopathic Terminology , AAOM, 2006)

"*Osteopathy is an established system of clinical diagnosis and manual treatment in which a caring approach to the patient and attention to individual needs are of primary importance.*
In particular, it is concerned with the interrelationship between the structure of the body and the way in which it functions and is therefore an appropriate form of therapy for many problems affecting the neuro-musculo-skeletal systems."(British Osteopathic Association, http://www.osteopathy.org/NJENQ851AI, 2007)

" Osteopathy is a 'whole body'system of manual therapy, based on unique biomechanical principles, which uses a wide range of techniques to treat musculo-skeletal problems and other functional disorders of the body."(Australian Osteopathic Association, http://www.osteopathic.com.au/index.php/about_osteopathy, 2007)

Osteopathic Manipulative Treatment

"The therapeutic application of manually guided forces by an osteopathic physician (US Usage) to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction." (Glossary of Osteopathic Terminology , AAOM, 2006)

Translational Medicine

is an emerging view of medical practice and interventional epidemiology, as a natural 21st century progression from Evidence-Based Medicine. It integrates research inputs from the basic sciences, social sciences and political sciences to optimise both patient care and also preventive measures which may extend beyond the provision of healthcare services. Practitioners, policy makers, and the public need sound evidence from different and new research methods, involving both experimental and non-experimental methodologies, that are sensitive to cultural and ethnic priorities.

Integrated training in translational research methods is needed in order to redress current biases in funding and research publications, in order to reflect better the balance of research efforts which are necessary for better assessment of complex evidence-bases, to integrate effective and culturally sensitive interventions with supporting environmental changes, and to encourage continuous improvement of evidence based public policies. (http://en.wikipedia.org/wiki/Translational_medicine, Jan 2010)

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I dedicate this project to all of my teachers past and present and, to my greatest teachers of all, my future patients.

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