

COMPLEMENTARY THERAPY SYSTEMS AND THEIR INTEGRATIVE EVALUATION

Gunver Sophia Kienle, MD,^{1,#} Hans-Ulrich Albonico, MD,^{2,3} Lorenz Fischer, MD,⁴ Martin Frei-Erb, MD,⁴ Harald J. Hamre, MD,¹ Peter Heusser, MME (UniBe),⁵ Peter F. Matthiessen, MD,⁶ Adrian Renfer, MD,⁷ and Helmut Kiene, MD¹

Complementary and alternative medicine (CAM) is becoming an integral part of modern medicine. Complementary and alternative medicine therapy systems include natural medicinal products, nonpharmacological treatments, and counselling on health and lifestyle issues. Complementary and alternative medicine concepts are often elaborate, transcending biophysical models and employing the principles of salutogenesis. Evaluations of CAM therapy systems need to be integrative and cover the dimensions of: (1) therapeutic professionalism; (2) patient perspective and public demand; (3) conceptuality; (4) safety, effectiveness, and costs. Complex research strategies are required, which reverse the phases of conventional drug assessment. The predominant use of randomized trials would introduce structural bias and create an artificial picture. Important are

evaluations of the whole system in real-world conditions, and surveys on component evaluations. Systemic CAM assessments should consist of a broad array of high-quality research methods: well-conducted randomized and nonrandomized studies, cohort studies, qualitative research, high-quality case reports and case series, studies on patient perspective, safety analyses, economic analyses, etc. Good clinical judgement, a core epistemic element of medicine based on nonstochastic principles, should also be integrated and could reflect routine patient care.

Key words: Complex Intervention, Evidence-based Medicine, Integrative Medicine, Research Methods, Whole System Research

(*Explore* 2011; 7:175-187. © 2011 Elsevier Inc. All rights reserved.)

INTRODUCTION

Complementary and alternative medicine (CAM) are key issues in the discussion on scientific evidence, clinical experience, medical judgment, and patient-focus in today's medicine.

Complementary and alternative medicine (CAM) methods usually transcend reductionist biophysical models, using a holistic approach to treat the patient. The goal is an extensive and sustainable cure or improvement, attained by the stimulation of salutogenetic self-healing processes. Treatment is highly individualized according to the needs of the patient, using natural medicinal products (of zoological, herbal, or mineral origin,

sometimes potentized), nonpharmacological therapies (eg, acupuncture, acupressure, neural therapy, movement therapies, art therapies, relaxation techniques, biofeedback, chiropractic, meditation, massage, lifestyle changes), and counseling. The physician-patient relationship is particularly important. The treatments are used in addition to conventional medicine ("complementary") or, in some cases, instead of it. Another term used, especially for research-based CAM systems, is *integrative medicine*.

The interest in CAM among patients is increasing worldwide, and physicians are also developing a favorable opinion toward many types of CAM.¹⁻¹⁴ In a state referendum in Switzerland in 2009, two-thirds of the population voted for the integration of CAM into the healthcare system.

Modern therapies should be effective, safe, and affordable within the healthcare system. Concerning CAM, the critical question therefore is: How can this be assessed while doing justice to scientific principles as well as to the complexity and the specific properties of CAM?

REVERSE RESEARCH STRATEGIES

The evaluation of effectiveness, safety, and costs plays a different role in CAM and in conventional drug therapy, because the two have developed in reverse directions: CAM consists of therapy systems with long traditions in patient care, evolved from distinct concepts, and looking back on times of experience that sometimes stretch over hundreds of years. Only secondary after such development in and from clinical practice, laboratory investigations, and clinical trials come in. Quite different is the situation for conventional drug therapies: they are primarily developed in the laboratory and then tested on animals and on

1 Institute for Applied Epistemology and Medical Methodology, Freiburg, Germany

2 Union of Associations of Swiss Physicians for Complementary Medicine, Luzern, Switzerland

3 Regional Hospital Emmental, Department of Complementary Medicine, Langnau, Switzerland

4 Institute of Complementary Medicine (KIKOM), University of Bern, Switzerland

5 Gerhard Kienle Chair for Theory of Medicine, Integrative and Anthroposophic Medicine, Center of Integrative Medicine, University of Witten/Herdecke, Germany

6 Department of Methodological Plurality in Medicine, Center of Integrative Medicine, University of Witten/Herdecke, Germany

7 Association of Swiss Medical Societies for Acupuncture and Chinese Medicine, Dietikon, Switzerland

Financial disclosure: We declare to have no conflict of interest.

Corresponding Author. Address.

Institute for Applied Epistemology and Medical Methodology, D-79111 Freiburg, Germany.

e-mail: gunver.kienle@ifaeimm.de

New isolated chemicals Conventional drug therapy	Health systems Complementary medicine
---	--

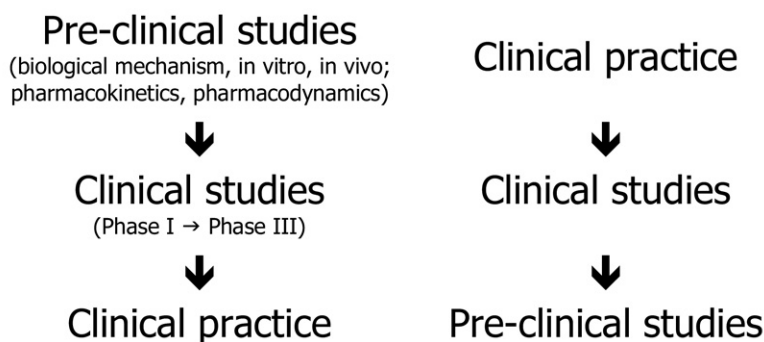


Figure 1. Reverse research strategies (adapted from ¹¹³).

humans in phase I-III studies. Only after this gatekeeping process they are introduced into clinical practice, which will then largely be guided by the study results. Coming from preclinical laboratory development, the remedies' therapeutic potential and safety in real-world practice are hardly calculable. This has led to drug tragedies, for example, the severe birth defects caused by the supposedly safe and popular sedative thalidomide,¹⁵ or the diethylene glycol poisoning known as the "Sulfanilamide tragedy."¹⁶ Therefore, clinical trials are the admission ticket to the clinical use of conventional drug therapy, and for this purpose the designs and guidelines of clinical research have been essentially delineated. As a consequence, for example, the members of the *International Conference on Harmonization (ICH)*, which issues the obligatory Good Clinical Practice (GCP)–Guidelines for clinical studies, consist of representatives of the pharmaceutical industry and of drug regulatory agencies.

Hence, for CAM and for conventional drug therapy, the approaches to clinical research follow reverse strategies (Figure 1).

EVIDENCE-BASED MEDICINE (EBM)

Clinical research evolved into EBM, its goal being to integrate best external evidence, individual clinical expertise, and patient perspective:¹⁷ patient treatment should be based on clinical research, and the jungle of research results published daily should be systematically processed and made accessible to the practitioners who search for up-to-date knowledge. This sensible *bottom-up* concept was, however, soon transformed into a *top-down* approach: EBM principles were incorporated into legislation and used for the increasing regulation of the medical profession and in this way also for decisions regarding the availability and reimbursement of therapies, thus marginalizing the role of clinical expertise and patient perspective.^{18,19} For this regulatory assessment, external evidence is hierarchically ordered. On top of the hierarchy is the randomized controlled trial (RCT), which is usually the only form of evidence accepted for regulatory decision making. Other research methods play at best a minor role, and clinical judgment has mostly been discredited, its potential power remaining unexplored and undeveloped.

There is no question that good clinical research and particularly RCTs make essential contributions to medicine and patient care. To integrate scientific evidence is an indispensable feature of medical professionalism, in conventional as well as in complementary medicine.^{20,21}

However, the crucial questions about EBM regard the issue of whether the organization of healthcare should be based primarily on certain types of clinical studies (namely RCTs); whether this type of "best evidence" allows reliable conclusions concerning the "best therapy" for the patient; and whether, for such conclusions, EBM's evidence-hierarchy offers substantial support or is potentially misleading.

These EBM principles, despite their far-reaching consequences for the healthcare system and despite the strict empirical self-conception of EBM, have not themselves been empirically evaluated as to whether disease outcomes are better when treatment follows hierarchical evidence (ie, comparing outcomes of patients treated primarily according to EBM guidelines and patients treated according to the physician's discretion).²² There are several hints that EBM is not necessarily advantageous for patients and costs: three large German RCTs investigated the influence of acupuncture on knee osteoarthritis, migraine, and low back pain compared to placebo acupuncture and to best evidence-based conventional therapy according to guidelines. Amazingly, in the case of knee osteoarthritis and low back pain, the best evidence-based conventional treatment was substantially inferior not only to acupuncture but also to the placebo therapy; there was a large and statistically highly significant effect difference (and for migraine, evidence-based therapy and placebo treatment were comparable).²³⁻²⁵ Even though these results are open to interpretation, they still show that the health benefit experienced by patients is not necessarily the greatest when applying RCT-oriented EBM. In a British cluster RCT, when patients with hypertension and type 2 diabetes were treated either according to guidelines or at the physicians' discretion, there was no difference in blood pressure control between the two groups after one year. However, the guideline group was more likely to receive higher doses of antihyperten-

Table 1. Factors That Can Lead to False-Negative Results in Randomized Controlled Trials⁵⁸⁻⁶⁰

- Therapy error, dosing error
- Adjunctive and compensatory treatment
- “Placebo” treatment with specific effects
- Dropouts/patient attrition and noncompliance
- Contamination and intention-to-treat analysis
- Informed consent
- Obsequiousness bias, social desirability bias
- Low discriminatory power of measurement instruments
- Tendency to give mediocre answers
- Group assimilation
- Low patient recruitment
- Conditioning effects
- Cognitive interactions
- Disturbance of physician-patient relationship
- Errors in attribution
- Simplified study design (mega studies)

sive drugs and had consulted physicians significantly more often.²⁶

Many physicians and clinical researchers are highly critical of the current outlook of EBM and its instrumentalization for regulatory purposes.^{22,27-42} They criticize: the one-sided focus on empiricism (which itself remains outside empirical evaluation and critical discourse); the narrow definition of evidence; the limited benefit for individual patients; the threat to the physician’s autonomy and clinical judgment; the impact on the physician-patient relationship; and EBM’s *top-down* revolution of the medical system, with overt totalitarian structures. Furthermore, they criticize the denigration of all other sources of knowledge such as the physicians’ clinical experience, tacit knowledge, and the patients’ observations, and also the failure to further investigate and assess the process of clinical learning and skill acquisition. They also regret that in the context of the overreaching RCT-alignment, diverse redefinitions occur: patient care transforms to “health technology”; healing and disease alleviation to “primary outcome measure”; physician to “provider”; and patient to “consumer.” Besides all, the medically necessary abilities of the art of treatment and of empathic engagement would continue to whither away.⁴³⁻⁴⁷

Critical attitude has grown also in EBM itself, with some of its representatives questioning the strict hierarchization of evidence: “Our main wish, from which all others stem, is that RCTs be taken off their pedestal, their exalted position at the top of an artificial evidence hierarchy; that all forms of evidence be appreciated for what they can offer . . . no single form of research is best. . . . We wish to see a diversity of research approaches, rather than a hierarchy.”⁴⁸

IS THE PRIORITIZATION OF RCTS RELIABLE FOR FINDING THE BEST THERAPY? (“BEST EVIDENCE” = “BEST THERAPY”?)

A basic assumption of EBM health policy is that the “best evidence” reflects the “best therapy available.” This conclusion,

however, is only valid if the conduction of RCTs is equally feasible for all potential therapies; if the RCTs are conducted under conditions similar to real-world clinical practice; and if RCT results are free from confounding factors—but these three preconditions are not generally met.

When designing RCTs, considerable efforts are made in order to avoid systematic bias affecting the comparison between intervention and control groups, particularly in order to avoid false-positive results. However, this does not mean that RCTs necessarily give an objective picture of therapeutic reality: the use of RCTs promotes some therapies and disadvantages others; the conduction of RCTs is fragile; and the results of RCTs have only limited applicability for clinical practice and leave important questions unanswered:

- The conduct of RCTs is only feasible for certain treatments because they require a number of preconditions: (1) *powerful financial backing*⁴⁹ (average costs per RCT with public health relevance are estimated at 12 million US dollars;⁵⁰ this is why RCTs are mostly sponsored by the financially strong pharmaceutical industry with the main goal of licensing and marketing of profitable therapies); (2) *academic attractiveness* (in order to increase the incentive to conduct and publish the trial); (3) *large numbers of patients*^{51,52} (because only a small fraction of available patients can be recruited, and various studies often compete for them); (4) *no preference* for either intervention or for control therapy⁵³ (because otherwise patients will not participate, and this is why, for instance, RCTs evaluating home versus hospital births cannot be conducted); (5) *equipoise*⁵⁴ (because a randomized assignment to the intervention or control group is unethical if the prospect for health benefit is unequal, and therefore, for instance, the efficacy of operative removal of a local malign gastrointestinal or gynecological tumor can generally not be investigated with RCTs); (6) *simple study protocols* (with simplified diagnostic and treatment procedures avoiding study complexity⁵⁵). (7) These limitations in the feasibility of RCTs give occasion for structural biases such as commercial bias, career bias, indifference bias and mediocrity bias. As a consequence, many therapies are disadvantaged: inexpensive therapies, nonpharmacological therapies, therapies for financially less promising patients, therapies with less attractiveness for those pursuing an academic career, therapies with an a priori obvious efficacy or with strong preferences, and also highly complex therapies—regardless of their actual therapeutic value for patients.⁵⁶
- The reliability of RCTs is not ensured by the design alone. Even in studies appearing to be methodologically perfect, results can still depend on imponderables such as the source of sponsoring.⁵⁷ RCTs on the same interventions often show substantial variation in results, as do corresponding systematic reviews and meta-analyses.⁵⁶ Moreover, RCT methodology is primarily devised (and sees its ethos in pursuing this goal) to avoid false-positive bias, but the protection against false-negative results receives hardly any attention. False-negatives often arise due to errors or to levelling out differences related to the disease, the treatment or the outcome assessment (see Table 1). They can be fostered but not avoided by randomization, blinding, and mega-trials. False-negative results lead to a

systematic underestimation of treatment effects in RCTs, and can often explain their small effect sizes.⁵⁸⁻⁶⁰

- The gap between the conditions of RCTs and real-world healthcare is widely recognized. This gap often arises from a considerable patient selection (eg, regarding disease severity, comorbidity, risk factors, gender, age, race, social status, cooperation, and expected treatment response; usually less than 1% of representative patients with the respective diagnosis are enrolled) or from differences in setting, diagnostic procedures, treatment, treatment goal, duration of treatment, follow-up, and adjunctive therapies. Therefore, RCT results have only limited applicability to routine clinical practice.^{52,56,61-65}
- The benefit of RCT-tested therapies for individual patients remains uncertain.³³ In RCTs, the “number [of patients] needed to treat” in order for one patient to finally receive benefit from the therapy, ranges between 2 and 250 patients. This means, conversely, that 50% to 99.6% of patients are treated needlessly (so-called “number treated needlessly” or “index of therapeutic impotence”⁶⁶) and cannot expect a benefit from the treatment. It is therefore essential to find ways to identify the patients who need different or additional treatment—a task left to the physician, who, for this purpose, needs to judge and to decide beyond the data from clinical studies.

The prioritizing of healthcare treatments according to the existence of respective RCTs leads to biased therapy selection and not necessarily to the selection of the best therapy for the patient. Therefore, in order to ensure optimal patient care, the physician himself must critically examine and evaluate the existing evidence. He must complement and even correct the external evidence by his own experience, internal evidence, professional knowledge, and by the patient perspective (Figure 2). Health authorities, as well, must appraise RCTs within their context. The authorities must also acknowledge that for therapies with long traditional use and large amounts of other evi-

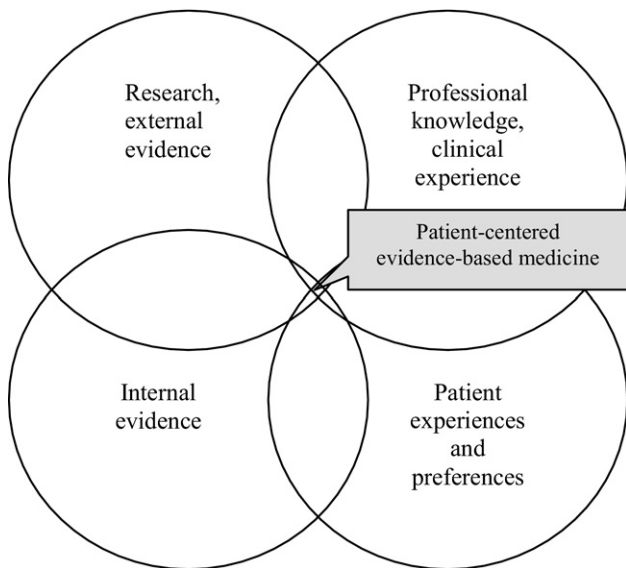


Figure 2. Four sources of evidence relevant for patient-centered, evidence-based medicine (adapted from ¹⁷⁵).

dence, RCTs are of limited informational value; and that, on the other hand, the physician’s discretionary and therapeutic freedom as well as his independent clinical judgment must be maintained.

Because the traditional use of RCTs does not reasonably address critical clinical questions faced by decision makers like physicians and patients or policy makers and purchasers, there is a need for research alternatives with a practical orientation, such as *pragmatic trials*^{67,68} or *comparative effectiveness research*.^{69,70} These studies, however, are complex and expensive. The costs of the ALLHAT study (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*⁷¹), for instance, comparing four therapies, amounted to 120 million US\$.⁷⁰ Such studies can only be conducted for selected clinical questions.

CONVENTIONAL MEDICINE BETWEEN EVIDENCE BASE AND CLINICAL JUDGMENT

Conventional medicine today—with its undeniable beneficial therapeutic innovations of the last century—stands between efficacy proofs based on external evidence and, on the other hand, good clinical judgment and its backing by pathophysiological reflections and basic epidemiological principles. Thus, even in a stronghold of clinical research such as the field of cardiology, only 11% of the recommendations in current authoritative guidelines (from the *American College of Cardiology* or the *American Heart Association*) are based on level A external evidence (RCTs, meta-analyses), whereas 48% are based on case studies, expert opinions or standards of care.⁷² The situation is similar in oncology: For 14 neoplastic hematologic disorders studied, only 24% of therapy recommendations were supported by level 1 evidence (RCTs), 21% by single-arm prospective studies (level 2), and 55% by retrospective or anecdotal evidence.⁷³ In the case of lung cancer, guideline recommendations are 29% evidence based and 71% consensus based.⁷⁴ Evidence from RCTs (level 1) is available primarily for initial interventions in newly diagnosed disease, hardly for relapsed or refractory disease.⁷³ Concerning surveillance and aftercare of patients having completed primary cancer treatment, external evidence is completely lacking,⁷⁵ and the effectiveness of surgical removal of local malignant tumors will probably never be proven through RCT comparisons of surgery versus no surgical intervention. Furthermore, systematic reviews used to build treatment guidelines for breast and colon cancer do not meet the required quality standards.⁷⁶ As an example for a common and often deadly infectious disease: the current WHO recommendations for the treatment of isoniazid-resistant tuberculosis, which are implemented in 90 countries, are not supported by a single RCT.⁷⁷

In many complex medical fields, evidence-based practice is only marginal and often critically questioned. In paediatric surgery—with its undeniable achievements—publications consist almost exclusively of case reports and case series, whereas RCTs are rare.⁷⁸ In palliative care, physicians see their practice as clearly not evidence based; with patients near death, the conduction of an RCT would bring about immense difficulties. Here, the focus lies not on RCT-testable, standardized treatments for specific diseases, but on the individualized care of the respective patient, addressing his particular needs, his suffering; therapy is

oriented toward the whole person, providing a comfortable, holistic environment for him or her. Anecdotal evidence, clinical judgement, intuition, and adaption to the patient are central; EBM evidence is secondary^{30,79} (“some people would say high-grade evidence is worse than what you see in front of you”⁷⁹). In the mental health field, evidence-based practice is the subject of vigorous controversy—whether the results from the clinical trials can be generally applied to individual patients, or can only be applied to a few standard situations for which clinicians choose the respective intervention anyway, with or without EBM algorithms.^{34,80}

Thus, in conventional medicine, RCTs only have a limited informational value, and other research methods as well as clinical judgment are equally important. Clinical judgment becomes essential whenever the treatment situation is complex; whenever the treatment outcome depends on the therapy provider’s skills; and whenever the focus is on individual patients and individual disease characteristics rather than on specific diagnoses—which are all frequent situations in medicine.

CLINICAL JUDGMENT AND MEDICAL PROFESSIONALISM

Clinical judgment is a core element of medical professionalism.^{20,21,81} In general, high expertise is characterized by excellent judgment, which develops from intelligence, knowledge, experience, and continuous critical reflection. Still—although “there is no substitute for excellent judgement”⁸²—in medicine the question arises: is judgment capable of reliably assessing therapy situations, and substantiating *internal* evidence? Or is it, rather, notoriously mistaken and dependent on external instruction? Can clinical judgment be a true adjunct to external evidence? What are the potentials of its development? These questions have only been investigated very little so far.

Today’s implicit model for medical professionalism is *technical rationality*.^{46,83}: intelligent practice is the application of scientific knowledge: the practitioner hands his unresolved practical problem over to the scientist, the scientist solves it and returns the new scientific knowledge to the practitioner who can then apply this knowledge in his practice. In this process, there appears to be no necessity for clinical judgment apart from the identification of the problems. The dominance of this model, conjunct with limited resources and with liability issues, leads to increasing external regulation of medical practice, to the decline of medical autonomy, to deprofessionalization, and to frustrated physicians.

Researchers on expertise see this model as grossly oversimplified. It fails to account for the heart of professionalism: for its complexity. At best the model suits the situation of novices.^{46,83-86} Experts and masters in all disciplines are in command of abilities beyond external knowledge:

- *Tacit knowledge*. This is a feature of competence and mastery. Experts know more than they can say, and therefore they often cannot sum up their outstanding decisions and actions into rules. If required to do so, they regress to novice level and to decreased expertise. Professional success is more strongly correlated to tacit knowledge than to conventional academic intelligence.^{84,86-89}

- *Reflection in action*. When the professional practitioner encounters problems or unexpected events for which external and tacit knowledge offer no immediate solution, he may respond by reflecting in action. The practitioner enters into a reflective dialogue with the situation in order to find new solutions, observing new phenomena, gaining new insights, and generating new knowledge. Experts have the ability of creative thinking, which has been the source for important discoveries, innovations and new medical insights. Today, this source of progress—this “spirit of innovation”—and its corrective against unsuited routine, is increasingly suppressed by excessive bureaucracy, formalization, and legal constraints and is pilloried by a plethora of negative attitudes.^{83,90-92}
- *Gestalt recognition*. A *gestalt* is the wholeness of a structure, recognizable independently from the characteristics of its parts.^{93,94} Gestalt recognition plays a major role in the acquisition of experience, in the development of tacit knowledge, and in experts’ judgments.^{86,87,90,95} In medicine, *gestalt* structures can be discerned when analyzing reliable clinical judgment, for example, on therapy effects or on adverse reactions (Table 2). The certainty of this kind of judgment increases with the complexity of the gestalt relations—as opposed to statistical conclusions from cohort comparisons.^{58,96}

In science itself, the epistemic virtues and the ideals of professionalism have undergone transformations in the 20th century, particularly in regard to the objectivity of knowledge: in the 19th century, the ideal of scientific objectivity was of a mechanical nature, with the guiding ideal of self-surveillance, self-denial, self-elimination, and the exclusion of any interpretation or other forms of “subjectivity,” favoring standardized and mechanical “blind sight” procedures. All attempts to extirpate subjectivity, however, failed. The automation of knowledge acquisition and the algorithmic judgment procedures ultimately got lost in incidental details, in an infinite complexity of variation and a multitude of artefacts, and were useless for pedagogy; furthermore, these techniques could often not be stringently applied or were unsuitable. Onward from the beginning of the 20th century, those ideals changed and were subordinated to the current leading scientific paradigm of professionalism. Now, the roots for scientific accuracy are seen in trained judgment, based on the

Table 2. Criteria of Gestalt-Based Therapy Judgement^{58, 96}

Strong criteria
- Space pattern correspondence
- Time pattern correspondence
- Morphological correspondence
- Dose-effect correspondence
- Ping-pong (dialogue) correspondence
- Functional therapeutic gestalt
- Functional therapeutic gestalt process
Weak criterion
- High pre/post time ratio

subjects' expertise, his trained instincts and intuition, self-confidence, experience, and on pattern recognition.⁹⁷

The competent, trained and critically reflected clinical judgment can, in principle, lead to reliable knowledge. It still has its place in the discovery of new therapeutic principles, as was recently demonstrated by the publication of a case study describing the surprising remission of pediatric hemangioma after application of the beta blocker propranolol; an effect that could be reliably reproduced in other children.⁹⁸ Discovery and explanation of therapies follow a distinct logic.⁹⁹ This is relevant also for CAM, because even though an abundance of scientific research is available on CAM, the physicians' and patients' own experience and judgment are often essential in the provision and further development of CAM therapies.

CLINICAL RESEARCH AND CAM

Complementary and alternative medicine is an area remarkable for its research activity: already in 2006 more than 20,000 controlled clinical studies were found in the relevant databases.^{100,101} There are plenty of blinded or open-label RCTs, well-conducted nonrandomized comparative studies, large healthcare studies, observational studies, safety studies, etc. A large body of preclinical research, Medline-indexed journals on CAM research, international congresses on CAM research, research organizations, academic centers, and a Cochrane Center specifically dedicated to the investigation of CAM also exist. "Evidence-based CAM" is a well-established term, and there is an intensive methodological debate on CAM research. CAM studies comply with the same methodological standards and go through the same scientific peer-review procedures as corresponding studies in conventional medicine. In direct comparisons, the methodological quality of CAM studies does not seem inferior to that of studies on conventional therapies.^{102,103}

Even though numerous RCTs have been conducted on CAM, they only have a selective or exemplary informational value for the assessment of CAM. One reason is the very large number of therapy options, due to the existence of several thousand medicinal products in different concentrations and dosage forms; of different nonpharmacological treatments; of extensive individual counselling on the current life situation, behavioral patterns, disease coping, and lifestyle; and of multiple modes of combination of these procedures for different patients and indications. Testing all would require hundreds of thousands or even millions of RCTs. Furthermore, RCTs usually do not mirror the real-world clinical practice and complexity of CAM: usually, in RCTs, the effect of a clearly defined and standardized intervention on predefined outcome parameters is studied, which provides information on the course of a likewise clearly defined disease. This presupposes that the disease can be clearly described, appears uniformly, can be treated with the same standardized intervention, and that its improvement can be measured with the same parameter. Even though many CAM procedures are being studied in this way, it is hardly consistent with their practical application:

CAM therapies do not focus on singular pathological processes but rather on the sick patient in his or her whole complexity, including physical, mental, spiritual, and social factors.

These are interconnected and need to be addressed in total and on multiple levels. Moreover, CAM therapies aim to support and stimulate autoprotective and (auto-)salutogenetic potentials, mostly with the active cooperation of the patient or of his/her organism (metaphorically speaking: "enabling the patient to swim"¹⁰⁴), rather than directly eliminating the disease or disease symptoms or directly correcting the pathological deviation in a patient being treated passively ("saving the drowning person"¹⁰⁴).¹⁰⁵ Salutogenetic approaches are more complex and need to be more individualized than the pathogenetic approach. Besides the patient's particular health situation, also his environment, family, culture, and socioeconomic factors have to be taken into account, as well as his individual resources that can be mobilized for more autonomy and sense of coherence.^{2,106} In people with same diagnoses, the salutogenetic potential and according therapy goals can be very divergent. Accordingly, the repertoire of CAM treatment is complex, and its application highly individualized.

CAM treatments and counseling are provided as integrative systems with interacting components. Accordingly, the effect of complex approaches often are larger than the sum of the components' effects. Therefore, testing isolated components often makes little sense; likewise the focus on single diseases (which often are treated differently in different patients) or on single outcome parameters (which often have different meaning for different people).

Therefore, CAM needs more broadly designed and more comprehensive research methods that study the intact, whole, and complex systems^{107,108} in order to mirror their real-world practice. These methods have been labelled *Whole System Research*,¹⁰⁹⁻¹¹¹ *CAM Systems Research*,^{112, 113} *Whole Medical Systems Research*,¹¹⁴ or *Complex Intervention Research*.^{115, 116} For example, it is recommended (Figure 3) first to assess the theoretical background and practical experience of the long-standing tradition, followed by safety assessment and then by a pragmatic evaluation of the whole system (as intact as possible), and only afterward to assess selectively isolated components and to elucidate exemplary mechanisms of action.¹¹³ This procedure is explicitly nonreductionist. It places less emphasis on the conduct of singular studies than on suitable research programs and nonhierarchical research networks that are cyclical, flexible, and adaptive and that encompass qualitative as well as quantitative methods.^{110,114}

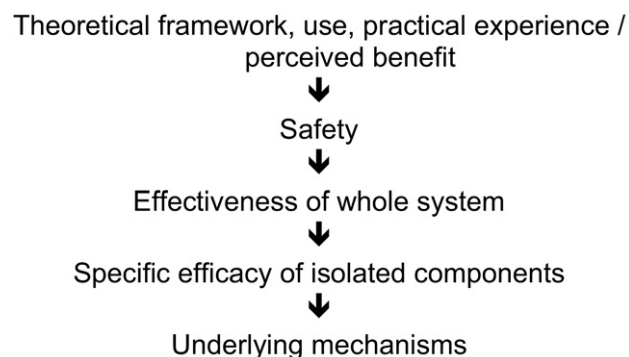


Figure 3. Researching complex health systems (adapted from ^{112,113}).

DOUBLE STANDARDS? A BRITISH DEBATE

Complementary and alternative medicine is often sweepingly criticized for not being “evidence-based,” “evident,” or even for obstructing scientific evaluation.¹¹⁷ Apart from the fact that this critique overlooks the existence of scientific studies, the question arises whether scientific data are at all capable of refuting this type of criticism. British social scientists describe a double standard in demanding evidence for CAM and conventional medicine: on one hand, British national cancer policy advocates, albeit implicitly, the integrative, patient-centered approach of CAM. On the other hand, the implementation of this policy as well as a constructive debate on evidence and effectiveness have been prevented by medical associations (British Medical Association, Royal College of Physicians). Paradigmatic and ideological barriers stand in the way, and insurmountable obstacles are created by using the term *evidence* very restrictively, despite the general acknowledgment that conventional medicine’s evidence base is limited as well and is often far below the required gold standard.⁷⁹ The considerable discrepancy between the ideal of EBM and the actual organizational practice easily leads to flexible and opportunistic adaptivity which is open to subjectivity, influence of medical stakeholders, political constellations, and the professional status and the persuasive power of the specialist. Strict evidence is primarily demanded when therapies are considered not appropriate and when the logic behind the therapy is questioned. The logic behind the therapy and the argumentation skills and societal influence of the proponents can be decisive in determining whether the so-called gold standard of evidence is demanded, or not. This all leads to a “black box” of funding decision making. As a consequence for CAM—which deviates from the mainstream rationales and is seen as a competitor—rigid evidence standards are demanded, as opposed to conventional medicine where these high standards are not universally implemented. This has been characterized as a “double standard,” used instrumentally to exclude CAM.^{79,118,119}

A rather interesting view of research evidence is presented by the patients: they see the research results as basically important and as not necessarily flawed, but they are largely sceptical of them, particularly when conventional scientists perform research on CAM. Quite generally they doubt that statistical results are of major relevance for their own case. They consider that average probabilities from clinical studies would not allow conclusions about their personal course of disease and about how they would react to treatment. Patients attribute large impact to lifestyle, emotion, and spirituality, and assume that this is not calculable by statistics. Complementary and alternative medicine treatments are chosen independently from the evidence base. More important are the patients’ own experiences of benefit, recommendations by his or her physicians, experiences by friends and family members, and the philosophical background of the therapy.^{79,120,121}

PLURALISTIC THERAPY APPROACH AND INTEGRATION OF CAM METHODS

Pluralism and dialogue are key principles for open and tolerant societies, and for the necessity of modern individualization.

Critical and constructive pluralistic discourse is the best protection against stagnation, fallacy, and totalitarianism. A key insight in 20th century theory of science was to acknowledge the pluralist structure of science—with its parallel systems both in mathematical as well as in empirical disciplines,¹²²⁻¹²⁵ with its pluralistic concepts of explanation,¹²⁶ its complementary¹²⁷ and competing¹²⁸ models, its multiple levels of understanding,¹²⁹ and its plurality of thought-styles and thought-collectives.¹³⁰⁻¹³² Accordingly, a pluralistic healthcare system^{105,133-136} supported by an ongoing critical discourse and scientific research, is the appropriate answer to the pluralistic structures of society and science, and the adequate response to the manifold diversities and complexities of disease.

For what reasons should CAM be accessible to patients?

1. Patients want CAM therapies to be available and find them helpful.^{1-5,12-14} Similarly, many physicians see the integration of CAM therapies as meaningful and useful.⁶⁻¹¹
2. Complementary and alternative medicine patients often suffer from chronic long-standing and severe illness^{121,137-149} and seek CAM when they do not or no longer respond (adequately) to conventional therapy; when a conventional therapy option is not available at all or is rejected out of inner convictions or preferences; or when conventional treatment is only symptomatic and not causal or healing, and symptom relief could also be attained through CAM methods.^{23-25,149}
3. Many patients and physicians want to avoid the side effects of conventional medical treatment. Drug side effects are the fourth to sixth leading cause of death in the United States,¹⁵⁰ also including drugs that often work only symptomatically (especially nonsteroidal anti-inflammatory drugs¹⁵¹) and could be replaced by CAM treatments. The almost routine administration of paracetamol to reduce fever in children with acute infections is associated with an increased risk for asthma, rhinoconjunctivitis, and eczema.¹⁵² and possibly reduces the development of immunity.¹⁵³ The treatment of such infections is one of the focuses of CAM. Similarly, the routine use of antibiotics for acute, often viral infections has long been criticized.^{154,155} Generally, our society is considered to be overmedicalized,^{156,157} which is a problem considering the potential side effects. Patients seeking CAM prefer to cut down on unnecessary medication.^{158,159} Although these issues are not resolved yet, they can nonetheless be a legitimate reason for patients to pursue their own differentiated decision regarding medical treatment.
4. Many patients do not understand their illness according to the biophysical model of conventional medicine but in a complex and holistic way.^{2,147,148,160} Accordingly, patients seek medical approaches that account for this complex and holistic understanding. Swedish cancer patients, as an example, perceived cancer care that is only concerned with the physical aspects of their disease and not with the mental and spiritual level as an additional injury (“a biomedical paradigm—viewing mind and body as separate—was sometimes perceived as a violation by the patients. . . . The women’s suffering was increased due to this inability of healthcare

providers to see them as persons, whole persons with feelings and thoughts”¹⁶¹).

5. Complementary and alternative medicine’s emphasis on lifestyle, the overall situation, and patient activity can be an asset to healthcare in general: especially in chronic diseases, the patient’s outcome, therapy response, well-being, and treatment compliance depend on cofactors such as nutrition, exercise, comorbidity, biographical features, lifestyle, family, and socioeconomics. The influence of these factors on widespread diseases such as diabetes, hypertension, and coronary disease is immense and in some areas considerably larger than the effects of drug treatment.^{106,162,163} An estimated 40% of premature deaths in the United States are due to an unhealthy lifestyle.¹⁶⁴ According to the INTERHEART study, the risk for myocardial infarction can be reduced by 90% to 94% by a healthier lifestyle,¹⁶⁵ whereas high-cost interventional procedures do not show additional benefit in RCTs.¹⁶⁶ To induce sustainable motivation for lifestyle changes, it is not a sufficient perspective only to inform about risk factor reduction (which is boring) or the risk of death (which is frightening, and therefore quickly blocked out). A key challenge is rather to develop individualized therapy concepts that have the capability to activate the patient’s own resources, individually considering his or her potentials, values, and environment. Strategies of life-

style change must be tailored to the individual patient in order to be feasible and to cause him to quickly feel much better and satisfied. Long-term compliance can then be maintained.¹⁰⁶

In this context fits the observation that CAM physicians have longer consultations with their patients than conventional physicians.^{140-144,167-169} Longer consultations are typical for patients with chronic disease, ill-defined problems, and social and psychological issues. On the other hand, longer consultations are associated with favorable outcomes, lifestyle, and prevention intervention, greater enablement and patient satisfaction, fewer prescriptions and referrals, less follow-up appointments and return visits, and also decreased stress for the physician.¹⁷⁰

Hence, a pluralistic therapy approach with the integration of CAM treatments—depending on the patients’ situation and preferences—can be a meaningful adjunct to conventional medicine.

INTEGRATIVE EVALUATION OF CAM

Evidence-based medicine defines itself as the integration of the best external evidence, individual clinical expertise, and patient perspective.¹⁷ This broad definition must be taken into account also on the regulatory level; otherwise, it will remain an empty phrase. Accordingly, therapy evaluation must be based on all of

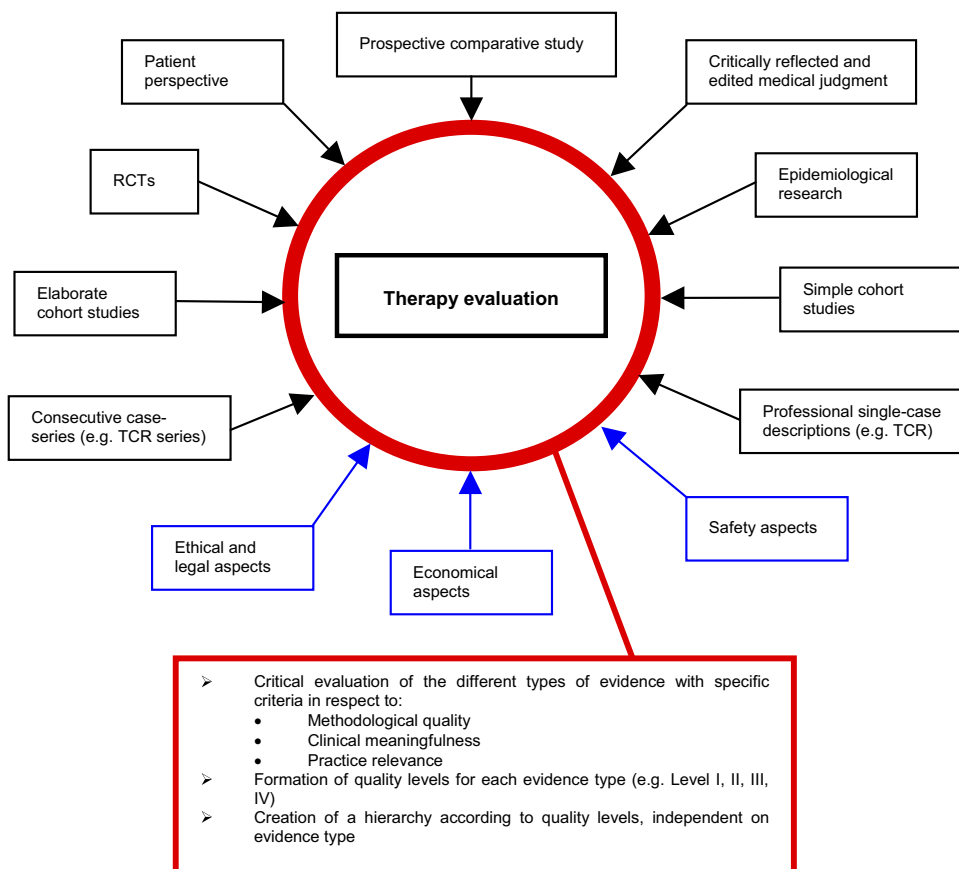


Figure 4. Information synthesis from different kinds of evidence.⁵⁶

it: external evidence, clinical expertise, and patient perspective. Furthermore, because CAM is not mainstream, additional questions arise concerning the conceptual background and therapeutic professionalism.²⁰

In case of external evidence (which includes the scientific evaluation of other physicians' clinical expertise), the evaluation of a complex therapy system used for decades or centuries is a different challenge than the evaluation of a single, newly synthesized drug. For the assessment of a whole therapy system, it is neither feasible nor meaningful to do RCTs on each single one of its medicinal products, and for every one of its potential indications and every one of its combinations with other relevant therapies. Also questionable would be to identify best research evidence just by the EBM-hierarchy of study designs. The evaluation of a CAM system should rather be based on the totality of the respective research material that should be critically examined regarding methodological quality, clinical meaningfulness, and practical relevance. These results can then be integrated into an overall synthesis (Figure 4).

Altogether, to adequately evaluate CAM systems, an integrative assessment system is needed. It should be able to answer the following questions:

1. *Therapeutic professionalism*: Does the treatment approach adhere to the criteria of professional treatment²⁰ and medical professionalism?²¹
2. *Patient perspective and public demand*: Do patients and citizens see the availability of the respective therapy system within the healthcare system as important? Is there a particular need for this kind of treatment?
3. *Conceptual basis*: What is the conceptual framework—within the respective *Denkstil* (thought style),¹³² paradigm,¹³⁰ *episteme*,¹⁷¹ construct¹⁷²⁻¹⁷⁴—of the therapy system, including its conception of man and nature, and how do these concepts relate to those of other therapy systems?
4. *Safety, effectiveness, costs*:
 - a. *Evaluation of the whole system*: Has the therapy system been evaluated as a whole and in real-world conditions? What are the results of these evaluation studies?
 - b. *Survey of component evaluations*: What are the results of studies of individual components, developed and used in the context of this therapy system? Exemplary areas of the therapy system should be evaluated by high-quality research (RCTs and well-designed nonrandomized comparative studies, meticulously conducted cohort studies, etc), whereas the bulk of other therapy options should be documented by the practitioners through transparent, high-quality case reports and case series, collected from routine patient care.

This total procedure implies the development of research programs. There is a necessity for the development of scientific expertise within the members of the respective CAM systems, for the assessment of the financial aspects of the necessary research projects, and for maintaining a construc-

tively critical dialogue between CAM and conventional medicine.

Acknowledgments

We are grateful for financial support by Christophorus Stiftungsfonds, Software-AG Stiftung Associations of Swiss Physicians for Complementary Medicine (UNION), EbiPharm, and Anthrosana.

REFERENCES

1. Molassiotis A, Fernandez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol*. 2005;16:655-663.
2. Ritchie J, Wilkinson J, Gantley M, Feder G, Carter Y, Formby J. *A Model of Integrated Primary Care: Anthroposophic Medicine*. London: National Centre for Social Research Department of General Practice and Primary Care, St. Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary, University of London. 2001:158.
3. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. *JAMA*. 1998;280:1569-1575.
4. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data*. 2004;343:1-19.
5. Featherstone C, Godden D, Selvaraj S, Emslie M, Took-Zozaya M. Characteristics associated with reported CAM use in patients attending six GP practices in the Tayside and Grampian regions of Scotland: a survey. *Complement Ther Med*. 2003;11:168-176.
6. Stange R, Amhof R, Moebus S. Complementary and alternative medicine: attitudes and patterns of use by German physicians in a national survey. *J Altern Complement Med*. 2008;14:1255-1261.
7. Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into family practices in Germany: results of a national survey. *Evid Based Complement Alternat Med*. 2009.
8. Furlow ML, Patel DA, Sen A, Liu JR. Physician and patient attitudes towards complementary and alternative medicine in obstetrics and gynecology. *BMC Complement Altern Med*. 2008;8:35.
9. Wahner-Roedler DL, Vincent A, Elkin PL, Loehrer LL, Cha SS, Bauer BA. Physicians' attitudes toward complementary and alternative medicine and their knowledge of specific therapies: a survey at an academic medical center. *Evid Based Complement Alternat Med*. 2006;3:495.
10. Manek N, Crowson C, Ottenberg A, Curlin F, Kaptchuk T, Tilburt J. What rheumatologists in the United States think of complementary and alternative medicine: results of a national survey. *BMC Complement Altern Med*. 2010;10:5.
11. Diehl V. The bridge between patient and doctor: the shift from CAM to integrative medicine. *Hematology*. 2009;2009:320-325.
12. Gray CM, Tan AW, Pronk NP, O'Connor PJ. Complementary and alternative medicine use among health plan members. A cross-sectional survey. *Effect Clin Pract*. 2002;5:17-22.
13. McCann LJ, Newell SJ. Survey of paediatric complementary and alternative medicine use in health and chronic illness. *Arch Dis Child*. 2006;91:173-174.
14. Härtel U, Volger E. Inanspruchnahme und Akzeptanz klassischer Naturheilverfahren und alternativer Heilmethoden in Deutschland—Ergebnisse einer repräsentativen Bevölkerungsstudie. *Forsch Komplementmed*. 2004;11:327-334.
15. Zichner L. *Die Contergankatastrophe-Eine Bilanz nach 40 Jahren*. Darmstadt: Steinkopff-Verlag; 2005.

16. Wax PM. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann Intern Med.* 1995;122:456-460.
17. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ.* 1996; 312:71-72.
18. Kienle GS. Evidenzbasierte Medizin und ärztliche Therapiefreiheit—Vom Durchschnitt zum Individuum. *Dtsch Arztebl.* 2008; 105:A1381-A1384.
19. Kienle GS. Bedeutet Evidence-based Medicine eine Abkehr von der ärztlichen Therapiefreiheit? In: Jütte RH, ed. *Die Zukunft der Individualmedizin.* Köln: Deutscher Ärzte-Verlag; 2009:69-77.
20. Kiene H, Brinkhaus B, Fischer G, et al. Professional treatment in the context of medical pluralism—A German perspective. *Eur J Integr Med.* 2010;2:53-56.
21. American Board of Internal Medicine, American College of Physicians—American Society of Internal Medicine, European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med.* 2002;136:243-246.
22. Saad A. The evidence-based paradox and the question of the Tree of Knowledge. *J Eval Clin Pract.* 2008;14:650-652.
23. Haake M, Muller HH, Schade-Brittinger C, et al. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *AMA Arch Intern Med.* 2007;167:1892.
24. Diener HC, Kronfeld K, Boewing G, et al. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurol.* 2006;5:310-316.
25. Scharf HP, Mansmann U, Streitberger K, et al. Acupuncture and knee osteoarthritis. *Ann Intern Med.* 2006;145:12-20.
26. Bebb C, Kendrick D, Coupland C, et al. A cluster randomised controlled trial of the effect of a treatment algorithm for hypertension in patients with type 2 diabetes. *Br J Gen Pract.* 2007;57:136-143.
27. von Wichert P. Evidenzbasierte Medizin (EbM): Begriff entideologisieren. *Dtsch Arztebl.* 2005;102:A-1569.
28. von Wichert P. Die unwirkliche Wirklichkeit der Medizin. *Dtsch Arztebl.* 2003;100:93-95.
29. Little M. "Better than numbers. . ." A gentle critique of evidence-based medicine. *ANZ J Surg.* 2003;73:177-182.
30. Rousseau P. Evidence-based medicine: show me the evidence! *Am J Hosp Palliat Care.* 2009;26:5-7.
31. Mykhalovskiy E. Evidence-based medicine: ambivalent reading and the clinical recontextualization of science. *Health.* 2003;7:331-352.
32. Miles A, Loughlin M, Polychronis A. Evidence-based healthcare, clinical knowledge and the rise of personalised medicine. *J Eval Clin Pract.* 2008;14:621-649.
33. Armstrong D. Professionalism, indeterminacy and the EBM project. *BioSocieties.* 2007;2:84.
34. Maier T. Evidence-based psychiatry: understanding the limitations of a method. *J Eval Clin Pract.* 2006;12:325-329.
35. Staller KM. Railroads, runaways & researchers: returning evidence rhetoric to its practice base. *Qual Inquiry.* 2006;12:503-522.
36. Traynor M. The oil crisis, risk and evidence-based practice. *Nurs Inq.* 2002;9:162-169.
37. Feinstein AR, Horwitz RI. Problems in the "vidence" of "vidence-based medicine." *Am J Med.* 1997;103:529-535.
38. Walker K. Why evidence-based practice now?: a polemic. *Nurs Inq.* 2003;10:145-155.
39. Shahar E. Does anyone know the road from a randomized trial to personalized medicine? A review of "Treating Individuals. From Randomized Trials to Personalised Medicine" Peter M. Rothwell. *J Eval Clin Pract.* 2008;14:726-731.
40. Holmes D, Murray SJ, Perron A, Rail G. Deconstructing the evidence-based discourse in health sciences: truth, power and fascism. *Int J Evid Based Healthcare.* 2006;4:180-186.
41. Holmes D, Perron A, O'Byrne P. Evidence, virulence, and the disappearance of nursing knowledge: a critique of the evidence-based dogma. *Worldviews Evid Based Nurs.* 2006;3:95-102.
42. Murray SJ, Holmes D, Rail G. On the constitution and status of evidence in the health sciences. *J Res Nurs.* 2008;13:272-280.
43. Kleinman A. The art of medicine. Catastrophe and caregiving: the failure of medicine as an art. *Lancet.* 2008;371:22-23.
44. Cox JL. Towards an evidence-based "Medicine of the Person": the contribution of psychiatry to health care provision. *J Eval Clin Pract.* 2008;14:694-698.
45. Lown B. *Die verlorene Kunst des Heilens.* Stuttgart: Schattauer Verlag; 2007.
46. Fish D, Coles C. *Developing Professional Judgement in Health Care.* Edinburgh: Butterworth-Heinemann; 2002.
47. Montgomery K. *How Doctors Think: Clinical Judgment and the Practice of Medicine.* New York, NY: Oxford University Press; 2006.
48. Jadad AR, Enkin MW. *Randomized controlled trials: questions, answers, and musings.* Malden, MA: Blackwell Publishing; 2007.
49. Bassand J-P, Martin J, Rydén L, Simoons M. The need for resources for clinical research: the European Society of Cardiology calls for European, international collaboration. *Lancet.* 2002;360:1866-1869.
50. Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS. Effect of a US National Institutes of Health programme of clinical trials on public health and costs. *Lancet.* 2006;367:1319-1327.
51. Horrobin DF. Are large clinical trials in rapidly lethal diseases usually unethical? *Lancet.* 2003;361:695-697.
52. Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trials apply?" *Lancet.* 2005;365: 82-93.
53. Ellis PM. Attitudes towards and participation in randomised clinical trials in oncology: a review of the literature. *Ann Oncol.* 2000; 11:939-945.
54. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med.* 1987;317:141-145.
55. Kotaska A. Inappropriate use of randomised trials to evaluate complex phenomena: case study of vaginal breech delivery. *Br Med J.* 2004;329:1036-1039.
56. Kienle GS. Gibt es Gründe für Pluralistische Evaluationsmodelle? Limitationen der Randomisierten Klinischen Studie. *Z ärztl Fortbild Qual Gesundh wesen.* 2005;99:289-294.
57. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Br Med J.* 2003;326:1167-1170.
58. Kiene H. *Komplementäre Methodenlehre der klinischen Forschung. Cognition-based medicine.* Berlin: Springer-Verlag; 2001.
59. Kiene H. A critique of the double-blind clinical trial. Part 1. *Altern Ther Health Med.* 1996;2:74-80.
60. Kiene H. A critique of the double-blind clinical trial. Part 2. *Altern Ther Health Med.* 1996;2:59-64.
61. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry.* 2002;159:469-473.
62. De Maeseneer JM, van Driel ML, Green LA, van Weel C. The need for research in primary care. *Lancet.* 2003;362:1314-1319.
63. Schulte M. Der Chirurg zwischen Leitlinien und Patientenindividualität. *Z ärztl Fortbild Qual Gesundh wesen.* 2005;99:321-323.
64. Travers J, Marsh S, Williams M, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax.* 2007;62:219-223.

65. Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *Milbank Q*. 2004;82:661-687.
66. Bogaty P, Brophy J. Numbers needed to treat (needlessly?). *Lancet*. 2005;365:1307-1308.
67. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis*. 1967;20:637-648.
68. MacPherson H. Pragmatic clinical trials. *Complement Ther Med*. 2004;12:136-140.
69. IOM (Institute of Medicine). *Initial National Priorities for Comparative Effectiveness Research*. Washington DC: The National Academies Press; 2009.
70. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290:1624-1632.
71. Davis BR, Cutler JA, Gordon DJ. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Anti-hypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997.
72. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301:831-841.
73. Djulbegovic B. The quality of medical evidence in hematology-oncology. *Am J Med*. 1999;106:198-205.
74. Harpole LH, Kelley MJ, Schreiber G, Toloza EM, Kolimaga J, McCrory DC. Assessment of the scope and quality of clinical practice guidelines in lung cancer. *Chest*. 2003;123:7S-20S.
75. Hölzel D, Schubert-Fritschle G. Evidenzbasierte Medizin in der Onkologie: spiegelt die Studienlage die klinische Realität wider? Evidence-based medicine in oncology: do the results of trials reflect clinical reality? *Zentralbl Chir*. 2008;133:15-19.
76. Vigna-Taglianti F, Vineis P, Liberati A, Faggiano F. Quality of systematic reviews used in guidelines for oncology practice. *Ann Oncol*. 2006;17:691-701.
77. Menzies D, Benedetti A, Paydar A, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. *PLoS Med*. 2009;6:e1000150.
78. Hardin WD, Stylianos S, Lally KP. Evidence-based practice in pediatric surgery. *J Pediatr Surg*. 1999;34:908-912.
79. Broom A, Tovey P. *Therapeutic Pluralism. Exploring the Experiences of Cancer Patients and Professionals*. London: Routledge; 2008.
80. Tanenbaum SJ. Evidence-based practice as mental health policy: three controversies and a caveat. *Health Aff*. 2005;24:163-173.
81. Royal College of Physicians. *Doctors in Society: Medical Professionalism in a Changing World. Report of a Working Party of the Royal College of Physicians of London*. London: Royal College of Physicians; 2005.
82. Miller JL. The complete cardiothoracic surgeon: qualities of excellence. *Ann Thorac Surg*. 2004;78:2-8.
83. Schön DA. *The Reflective Practitioner. How Professionals Think in Action*. New York: Basic Books; 1983.
84. Neuweg GH. *Könnerschaft und implizites Wissen*. 3. Auflage ed. Münster: Waxmann Verlag GmbH; 2004.
85. Wieland W. *Überlegungen zur Medizinteorie*. Berlin: Walter de Gruyter; 1975.
86. Ericsson KA, Charness N, Feltovich PJ, Hoffmann RR, eds. *The Cambridge Handbook of Expertise and Expert Performance*. Cambridge, MA: Cambridge University Press; 2006.
87. Polanyi M. *The Tacit Dimension (1966)*. Gloucester, MA: Peter Smith; 1983.
88. Dreyfus HL, Dreyfus SE. Expertise in real world contexts. *Organ Stud*. 2005;26:779-792.
89. Henry SG. Recognizing tacit knowledge in medical epistemology. *Theor Med Bioeth*. 2006;27:187-213.
90. Gruber H, Ziegler A, Hrsg. *Expertiseforschung*. Opladen: Westdeutscher Verlag; 1996.
91. Shaywitz DA, Ausiello DA. Preserving creativity in medicine. *PLoS Med*. 2004;1:e34.
92. Horrobin DF. Effective clinical innovation: an ethical imperative. *Lancet*. 2002;359:1857-1858.
93. von Ehrenfels C. Über Gestaltqualitäten. *Vierteljahresschr Wiss Philos*. 1890;14:249-292.
94. Wertheimer M. Untersuchungen zur Lehre der Gestalt. Teil 1. *Psychol Forsch*. 1922;1:47-58.
95. Larkin J, McDermott J, Simon DP, Simon HA. Expert and novice performance in solving physics problems. *Science*. 1980;208:1335-1342.
96. Kiene H. Was ist Cognition-based Medicine? *Z ärztl Fortbild Qual Gesundh wesen*. 2005;99:301-306.
97. Daston L, Galison P. *Objectivity*. New York: Zone Books; 2007.
98. Léauté-Labrèze C, de la Roque D, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358:2649-2651.
99. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med*. 2008;5:e67.
100. Saller R. Komplementärmedizin. Grundbedürfnis oder Luxus? Tagung der SGGP, 3. Available at: http://www.sggp.ch/tagungen/tagung/mai03_07.cfm. Accessed May 2007.
101. Saller R. Evidenzbasiert—für die Komplementärmedizin ein Fremdwort? “Und” statt “oder.” In: *Die Komplementärmedizin im Fokus*. München: Elsevier GmbH; 2006.
102. Shang A, Huwiler-Müntener K, Nartey L, et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet*. 2005;366:726-732.
103. Nartey L, Huwiler-Müntener K, Shang A, Liewald K, Jüni P, Egger M. Matched-pair study showed higher quality of placebo-controlled trials in Western phytotherapy than conventional medicine. *J Clin Epidemiol*. 2007;60:787-794.
104. Antonovsky A. *Salutogenese*. Tübingen: Dgvt Verlag; 1997.
105. Matthiessen PF. Paradigmenpluralität und ärztliche Praxis. In: Jütte RH, ed. *Die Zukunft der Individualmedizin*. Köln: Deutscher Ärzte-Verlag; 2009:37-53.
106. IOM (Institute of Medicine). *Integrative Medicine and the Health of the Public: A Summary of the February 2009 Summit*. Washington, DC: The National Academies Press; 2009.
107. IOM (Institute of Medicine). *Integrative Medicine Research: Context and Priorities. Commissioned for the IOM Summit on Integrative Medicine and the Health of the Public February, 2009*. Washington, DC: IOM (Institute of Medicine); 2009.
108. Fønnebo V, Grimsgaard S, Walach H, et al. Researching complementary and alternative treatments—the gatekeepers are not at home. *BMC Med Res Methodol*. 2007;7:7.
109. Ritenbaugh C, Verhoef M, Fleishman S, Boon H, Leis A. Whole systems research: a discipline for studying complementary and alternative medicine. *Altern Ther Health Med*. 2003;9:32-36.
110. Verhoef MJ, Lewith G, Ritenbaugh C, Boon H, Fleishman S, Leis A. Complementary and alternative medicine whole systems research: beyond identification of inadequacies of the RCT. *Complement Ther Med*. 2005;13:206-212.
111. Verhoef MJ, Leis A. From studying patient treatment to studying patient care: arriving at methodologic crossroads. *Hematol Oncol Clin North Am*. 2008;22:671-682.
112. Fønnebo V, Grimsgaard S. Alternativ medisin—hvordan vil fremtiden se ut? [Alternative medicine—What will the future look like?]. *Tidsskr Nor Lægeforen*. 2004;124:673.

113. Fønnebo V, Grimsgaard S, Walach H, et al. Researching complementary and alternative treatments—the gatekeepers are not at home. *BMC Med Res Methodol*. 2007;7:7.
114. Boon H, MacPherson H, Fleishman S, et al. Evaluating complex healthcare systems: a critique of four approaches. *Evid Based Complement Alternat Med*. 2007;4:279-285.
115. Campbell NC, Murray E. Designing and evaluating complex interventions to improve health care. *Br Med J*. 2007;334:455.
116. Anderson R. New MRC guidance on evaluating complex interventions. *BMJ*. 2008;337:a1937.
117. Lüscher TF. Ist die Medizin von Sinnen? *Kardiovaskuläre Med*. 2009;12:277-281.
118. Kelner M, Wellman B, Boon H, Welsh S. Responses of established healthcare to the professionalization of complementary and alternative medicine in Ontario. *Soc Sci Med*. 2004;59:915-930.
119. Walach H. The campaign against CAM—a reason to be proud. *J Holistic Healthcare*. 2009;6:8-13.
120. Verhoef MJ, Mulkins A, Carlson LE, Hilsden RJ, Kania A. Assessing the role of evidence in patients' evaluation of complementary therapies: a quality study. *Integr Cancer Ther*. 2007;6:345-353.
121. Wapf V, Busato A. Patients' motives for choosing a physician: comparison between conventional and complementary medicine in Swiss primary care. *BMC Complement Altern Med*. 2007;7:41.
122. Hilbert D, Ackermann W. *Grundzüge der theoretischen Logik [Erstausgabe 1928]*. Berlin: Springer-Verlag; 1988.
123. Hilbert D, Bernays P. *Grundlagen der Mathematik [Erstausgabe 1934]*. Berlin: Springer-Verlag; 1968.
124. Filler A. *Euklidische und nichteuklidische Geometrie*. Heidelberg: Spektrum Akademischer Verlag; 1993.
125. Heisenberg W. *Der Teil und das Ganze*. 4. ed. München: Piper; 1972.
126. Godfrey-Smith P. Explanation. In: Godfrey-Smith P, ed. *Theory and Reality. An Introduction to the Philosophy of Science*. Chicago, IL: University of Chicago Press; 2003:190-201.
127. von Weizsäcker CF. Komplementarität und Logik. In: Weizsäcker CF, ed. *Zum Weltbild der Physik*. Stuttgart: Hirzel-Verlag; 1990:281-331.
128. Lakatos I. Falsification and the methodology of scientific research knowledge. In: Lakatos I, Musgrave G, eds. *Criticism and the Growth of Knowledge*. Cambridge, MA: Cambridge University Press; 1970: 91-195.
129. Nicolis G, Prigogine I. *Die Erforschung des Komplexen. Auf dem Weg zu einem neuen Verständnis der Naturwissenschaften*. München: Piper; 1987.
130. Kuhn TS. *The structure of scientific revolutions*. Chicago, IL: The University of Chicago Press; 1996.
131. Spinner H. *Pluralismus als Erkenntnismodell*. 1 ed. Frankfurt am Main: Suhrkamp; 1974.
132. Fleck L. *Genesis and Development of a Scientific Fact*. Chicago, IL: University of Chicago Press; 1979.
133. Jütte RH. *Die Zukunft der Individualmedizin. Autonomie des Arztes und Methodenpluralismus*. Köln: Deutscher Ärzte-Verlag; 2009.
134. Willich SN, Girke M, Hoppe J-D, et al. Schulmedizin und Komplementärmedizin: Verständnis und Zusammenarbeit müssen vertieft werden. *Dtsch Arztebl*. 2004;101:A1314-A1319.
135. Kiene H, Ollenschläger G, Willich SN. Schwerpunkt: Pluralismus in der Medizin - Pluralismus der Therapieevaluation? *Z ärztl Fortbild Qual Gesundb wes*. 2005;99:261-323.
136. Pluralität in der Medizin. *Der geistige und methodische Hintergrund. Bericht über ein Symposium der Medizinisch Pharmazeutischen Studiengesellschaft e.V.* vom 24.-26. Mai 1979 in Titisee/Schwarzwald. Frankfurt am Main: 1980.
137. von Rohr E, Pampallona S, van Wegberg B, et al. Attitudes and beliefs towards disease and treatment in patients with advanced cancer using anthroposophical medicine. *Onkologie*. 2000;23: 558-563.
138. Carlsson M, Arman M, Backman M, Flatters U, Hatschek T, Hamrin E. Evaluation of quality of life/life satisfaction in women with breast cancer in complementary and conventional care. *Acta Oncol*. 2004;43:27-34.
139. Busato A, Dönges A, Herren S, Widmer M, Marian F. Health status and health care utilisation of patients in complementary and conventional primary care in Switzerland—an observational study. *Fam Pract*. 2006;23:116.
140. Marian F, Joost K, Saini KD, von Ammon K, Thurneysen A, Busato A. Patient satisfaction and side effects in primary care: an observational study comparing homeopathy and conventional medicine. *BMC Complement Altern Med*. 2008;8:52.
141. Schoeni-Affolter F, Matter-Walstra K, Widmer M, Busato A. Satisfaction with primary health care in patients with upper respiratory tract infection: a three-level approach. *Forsch Komplementmed*. 2007;14:346-352.
142. Esch BM, Marian F, Busato A, Heusser P. Patient satisfaction with primary care: an observational study comparing anthroposophic and conventional care. *Health Qual Life Outcomes*. 2008; 6:74.
143. Michlig M, Ausfeld-Hafter B, Busato A. Patient satisfaction with primary care: a comparison between conventional care and traditional Chinese medicine. *Complement Ther Med*. 2008;16:350-358.
144. Mermoud J, Fischer L, Staub L, Busato A. Patient satisfaction of primary care for musculoskeletal diseases: a comparison between neural therapy and conventional medicine. *BMC Complement Altern Med*. 2008;8:33.
145. Pampallona S, von Rohr E, van Wegberg B, et al. Socio-demographic and medical characteristics of advanced cancer patients using conventional or complementary medicine. *Onkologie*. 2002; 25:165-170.
146. Al Windi A. Determinants of complementary alternative medicine (CAM) use. *Complement Ther Med*. 2004;12:99-111.
147. Astin JA. Why patients use alternative medicine. Results of a national study. *JAMA*. 1998;279:1548-1553.
148. Sirois FM. Motivations for consulting complementary and alternative medicine practitioners: a comparison of consumers from 1997-8 and 2005. *BMC Complement Altern Med*. 2008;8:16.
149. Rao JK, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M. Use of complementary therapies for arthritis among patients of rheumatologists. *Ann Intern Med*. 1999;131:409-416.
150. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA*. 1998;279:1200-1205.
151. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340: 1888-1899.
152. Beasley R, Clayton T, Crane J, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet*. 2008;372:1039-1048.
153. Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009;374:1339-1350.
154. Huttner B, Goossens H, Verheij T, Harbarth S. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis*. 2010;10:17-31.

-
155. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365:579-587.
156. Moynihan R, Cassels A. *Selling Sickness*. New York, NY: Nation Books; 2006.
157. Angell M. *The Truth about Drug Companies*. New York: Random House; 2004.
158. Hamre HJ, Fischer M, Heger M, et al. anthroposophic vs. conventional therapy of acute respiratory & ear infections: a prospective outcomes study. *Wien Klin Wochenschr*. 2005;117:258-268.
159. Haidvogel M, Riley DS, Heger M, et al. Homeopathic and conventional treatment for acute respiratory and ear complaints: a comparative study on outcome in the primary care setting. *BMC Complement Altern Med*. 2007;7:7.
160. Steinsbekk A, Launso L. Empowering the cancer patient or controlling the tumor? A qualitative study of how cancer patients experience consultations with complementary and alternative medicine practitioners and physicians, respectively. *Integr Cancer Ther*. 2005;4:195-200.
161. Arman M, Rehnsfeldt A, Lindholm L, Hamrin E. The face of suffering among women with breast cancer—being in a field of forces. *Cancer Nurs*. 2002;25:96-103.
162. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or Metformin. *N Engl J Med*. 2002;346:393-403.
163. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206-1252.
164. Volpp KG, Das A. Comparative effectiveness—thinking beyond medication A versus medication B. *N Engl J Med*. 2009;361:331-333.
165. Yusuf S, Hawken S, Èunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952.
166. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
167. Busato A, Schöni-Affolter F. Ambulante medizinische Versorgung von Kindern in der Schweiz—ein Vergleich zwischen konventioneller und komplementärer Medizin. *Prim Care*. 2008;8:63-65.
168. Matter-Walstra K, Schoeni-Affolter F, Widmer M, Busato A. Patient-based evaluations of primary care for cardiovascular diseases: a comparison between conventional and complementary medicine. *J Eval Clin Pract*. 2008;14:75-82.
169. Heiligers P, de Groot J, Koster D, van Dulmen S. Diagnoses and visit length in complementary and mainstream medicine. *BMC Complement Altern Med*. 2010;10:3.
170. Sturmberg JP, Cilliers P. Time and the consultation an argument for a “certain slowness.” *J Eval Clin Pract*. 2009;15:881-885.
171. Foucault M. *Les Mots et les Choses. Une Archéologie des Sciences Humaines*. Paris: Bibliothèque des sciences humaines; 1966.
172. Brown TL. *Making Truth*. Urbana, IL: University of Illinois Press; 2008.
173. Lakoff G, Johnson M. *Metaphors We Live By*. Chicago, IL: University of Chicago Press; 1980.
174. Von Glasersfeld E. *Radical Constructivism: A Way of Knowing and Learning*. United Kingdom: Falmer Press; 1996.
175. Rycroft-Malone J, Seers K, Titchen A, Harvey G, Kitson A, McCormack B. What counts as evidence in evidence-based practice? *J Adv Nurs*. 2004;47:81-90.