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Applying Evidence to Support Ethical Decisions: Is the Placebo Really Powerless?

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ABSTRACT: *Using placebos in day-to-day practice is an ethical problem. This paper summarises the available epidemiological evidence to support this difficult decision. Based on these data we propose to differentiate between placebo and "knowledge framing". While the use of placebo should be confined to experimental settings in clinical trials, knowledge framing – which is only conceptually different from placebo – is a desired, expected and necessary component of any doctor-patient encounter. Examples from daily practice demonstrate both, the need to investigate the effects of knowledge framing and its impact on ethical, medical, economical and legal decisions.*

The management of health-care expenditures is one of the important societal problems in many countries. Several factors, such as increasing life expectancy, the unemployment rate, progress in medicine, and the increase in demanded and provided medical services are discussed as possible reasons for this economic dilemma. Among

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these the increasing utilization of the health-care systems by many of its stakeholders may be a central problem worth addressing. Politicians have made various attempts to solve this problem. Most of these approaches have addressed the modulation of costs or reimbursement of services, but have not included a critical appraisal of the consequences, i.e., critically analyzing the values of the provided services. Only recently the UK established an independent scientific institute, The National Institute of Clinical Excellence (NICE), which is supposed to describe the individual patient's and societal values of health-care interventions. These values will be the basis for political decisions.[a]

Twenty-five years ago, Green[1] described seven dilemmas of evaluation and measurement posed by the nature of health education. One of these problems is the understanding and differentiation of "true experimental" and placebo effects. Despite a large volume of recent data,[2,3,4,5,6,7,8] mainstream medicine is not yet prepared to discuss the possible significance of its own placebo effects, but accepts the concept of placebo to explain effects of "complementary" or "alternative" medicine. It is essential for scientists who support political decisions to recognize the importance of the recent revision of §29 of the Declaration of Helsinki.[9] This revision permits a wider use of placebo in scientific medicine, i.e., the use of placebo even if an approved treatment is available. This decision will contribute to a better understanding of placebo effects.

In this paper, we discuss the hypothesis that the unwanted placebo effect in clinical trials may be a desired effect in day-to-day practice. The conceptual differences between unwanted treatment effects in clinical trials (placebo effects) and desired treatment effects in day-to-day practice ("knowledge framing") are discussed. A model of three components of any therapeutic intervention is proposed, and possible consequences for the design of future clinical trials, as well as for ethical decisions and economical evaluations, are considered.

Methods

In the first part of this paper, we describe two sources of evidence which stimulated our hypothesis that the information given to patients at several steps in a clinical trial (information provided before obtaining informed consent and later before beginning treatment) may influence the observed result. The first source of evidence is derived from a study on adjuvant treatment of colorectal cancer with the monoclonal antibody 17-1A.[10] The second source is derived from our meta-analysis on immunotherapy of advanced renal cell cancer.[11,12]

In the second part, we discuss methodical problems that may induce placebo effects ("knowledge framing") and which may incorrectly be interpreted as pharmacological effects. Such evidence was obtained from two workshops with participants from various fields of medicine, including public health, biometrics, and

a. Concepts, methods and examples of the evaluation of health-care services from the patient's and a societal point of view ("Clinical Economics") were recently summarized.[13]

medical ethics, who completed a critical appraisal of the Hróbjartsson's and Goetzsche's meta-analysis on the power of placebo effects.[2]

In the third part, a model of the components of a placebo therapy is described. The model was developed based on the results of the above analyses. Its possible applicability to any treatment intervention is discussed. Finally, possible consequences for ethical decisions and for the design and conduct of future clinical trials are discussed.

Results

The hypothesis of "Knowledge Framing"

The first part of this evidence was derived from a clinical trial which investigated the effect of the adjuvant[b] treatment of colorectal cancer with the monoclonal antibody 17-1A.[10] The investigators performed a randomised study comparing the survival of patients who received with those who did not receive the monoclonal antibody following complete surgical resection of their primary tumors. As it is difficult to recruit patients to a study offering a promising treatment in only one arm of the trial, Zelen developed a special study design to increase the number of participating patients.[14] According to this protocol, patients were randomised to a treatment or a no-treatment group before obtaining informed consent. Following randomisation, informed consent was obtained only from the patients in the treatment group. No informed consent was considered necessary from the patients in the no-treatment group, as these patients were treated according to the current standard. The protocol was approved by the institutional review board. We are aware of the ethical problem associated with this decision, but we shall address another aspect associated with this type of randomisation.

As a result of this study, a large and significant survival advantage was demonstrated in the group of patients treated with adjuvant therapy. Confirmatory studies were not published.

Figure 1 (**p. xx**) shows that patients in the treatment group received two types of interventions, a pharmacological treatment (monoclonal antibody) and a psycho-social intervention (information about a treatment which is expected to reduce the rate of recurrent disease). The interpretation of the favourable outcome of this experiment is difficult, as either the pharmacological or the psycho-social or both interventions may have caused the effect. A subsequent experiment, which included the monoclonal antibody but did not leave the control group un-treated has not been reported Although the pharmacological effects of this antibody are no longer being investigated, it is worthwhile analysing the published data.

The second source of evidence which induced the concept of knowledge framing was supported by our systematic review of immunotherapy for advanced renal-cell cancer (RCC) published in the Cochrane Library.[11] The specific hypotheses were: (1):

b. Adjuvant treatment is given to patients who are at risk of recurrent disease following complete surgical resection of the primary tumour.

high-dose IL-2, the approved treatment option in the USA, results in longer survival than other options, and (2): IFNα, the most frequently-used option in other countries, produces longer survival than other options. The review was prepared according to standard criteria for systematic review as outlined in the handbook of the Cochrane Collaboration.

A total of 98 references to 58 randomised trials were assessed. 42 trials, involving a total of 4216 patients, fulfilled the inclusion criteria for acceptance in the systematic review. Based on the remission rates from 10 studies and the survival data from 6 studies of interferon-α, we were able to demonstrate that IFNα significantly reduced the one-year mortality as compared to controls who received no immunotherapy. The odds ratio of this successful treatment was 0.67 (95% CI 0.50-0.89). This effect corresponded to an increase in survival by 2.6 months. In reconsidering the data shown in Figure 2, we felt that there are too few epidemiological criteria to conclude a causal relationship between IFNα treatment and prolongation of survival in advanced RCC. The observed effect is not specific, as different immunotherapies induce similar, although not statistically significant, effects; the lack of statistical significance may be due to small sample sizes). There is no convincing biologic plausibility for IFNα and, finally, data supporting a possible dose-response relationship between IFNα and survival are missing.

To demonstrate specificity, an experiment should compare IFNα versus other immunotherapies versus non-immunotherapy and show that only IFNα, but not the other immunotherapies, prolongs survival. This experiment, however, has not been conducted. The lack of methodological quality and the epidemiological weakness was recognised in our Cochrane review, but not accorded sufficient importance. This led to the conventional interpretation of the results, concluding that IFNα prolongs survival in patients with advanced RCC. Considering these epidemiological problems and the large variance in survival reported in different randomised trials (which considerably exceeds the survival variance induced by treatment interventions) (Figure 2), we concluded that IFNα is associated with prolonged survival, but is not necessarily the cause of this effect. A different interpretation of the results is that IFNα, like any other immunotherapy, seems more promising to the physician, who then expects a more favourable patient outcome than without immunotherapy.

In part, our reinterpretation depends on observations in a number of small randomised trials which lack the power to reach definitive conclusions. Therefore, our concept of the impact of immunotherapy on survival is a hypothesis worthy of further investigation. In our previous example, we used the term “knowledge framing” to describe these desired effects and avoid the negative connotation which might be associated with the term “placebo”.

Figure 1: Zelen's design: Patients are randomized to either an "active-treatment" group or a "no-treatment" group before obtaining informed consent. Following randomisation, informed consent was obtained from patients in the active-treatment group. The arrows indicate that patients in the active-treatment group received two types of interventions, a pharmacological treatment (active treatment) and a psycho-social intervention (induction of hope and development of a future perspective mediated by the informed consent).

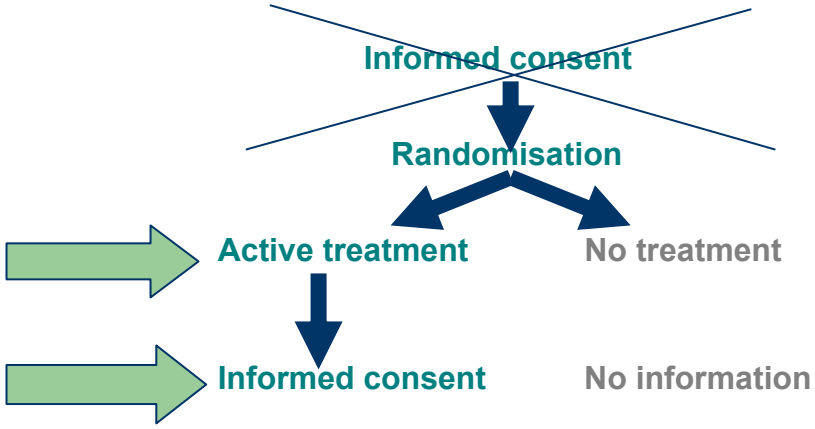
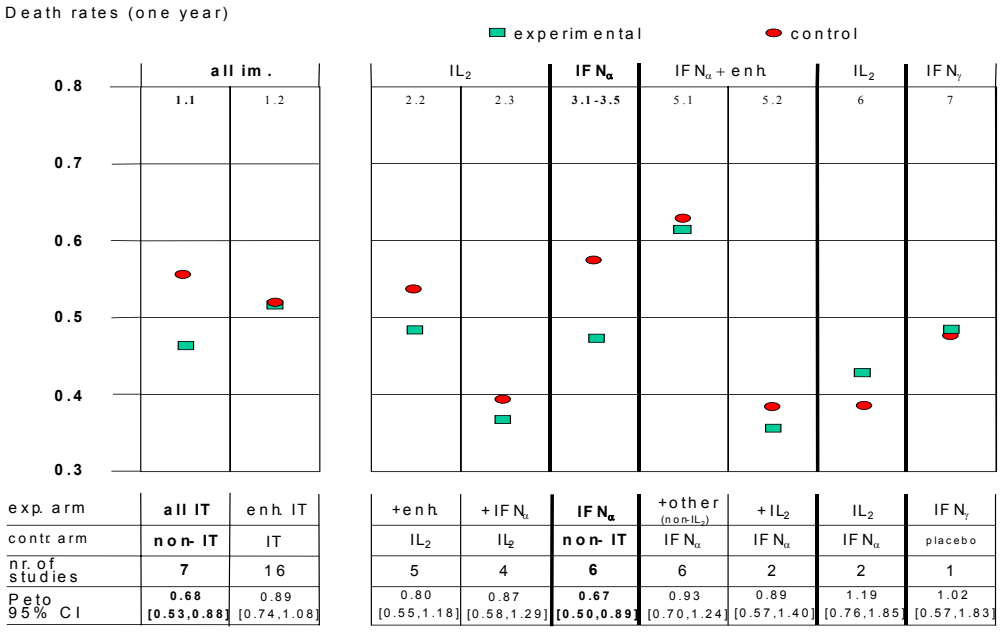


Figure 2: Deaths rates at one year for all included studies reporting survival (1.1 and 1.2) and for different subgroups classified by treatments (2.2 to 7). Numbers and grouping are identical with our Cochrane Review "Immunotherapy for advanced renal cell cancer". Green rectangles represent death rates in experimental groups, red circles represent death rates in controls. The treatments of experimental as well as control groups, the numbers of included studies per group and the Peto odds ratios including the 95% confidence intervals are shown. Subgroups showing significant differences between treatment arms are marked by bold letters.



Induction of "Knowledge Framing"

This section summarizes features of clinical trials which may induce the effect of "knowledge framing". The described features were detected in a critical appraisal of a meta-analysis[2] investigating the power of placebo. These features are: informed consent, study design, importance of findings, and conclusions drawn.

Informed consent

It has been shown in the above section that the information provided to the patients is a potentially powerful factor which may influence the treatment outcomes. Therefore, the information provided to patients should be standardized. One possible way to address this problem is standardization of informed consent. A standardized informed consent could be advantageous from an ethical and an epidemiological point of view. Using the example of a meta-analysis, we demonstrate that the effects of the patient information are difficult to interpret in studies which include three groups, an active treatment group, a no-treatment group and a placebo group.

If the patients are informed before randomisation, many will refuse to participate in such a study to avoid the risk of not being treated. Different problems emerge with patients who agree to participate in such a trial. These problems will are discussed below.

The doctor who informs the patients may also contribute to the variation in the experimental condition, as it is difficult to provide exactly the same information to patients who will be treated and to those who will not. There is a high risk that these two groups of patients receive different, "socially desired" information from the doctor. We therefore claim that this type of three-armed study is not sufficiently standardised to produce reliable results. Our criticism is based on the assumption that it is almost impossible to include active treatment, no treatment and placebo treatment in a single clinical trial unless the presently-accepted ethical and epidemiological criteria for clinical trials are "adapted". For example, patients who know that they are allocated to the untreated study group are at high risk of dropping out or seeking treatment outside of the trial.

Study design, including blinding

To investigate the power of placebo, three-armed studies were included in the meta-analysis. The treatment arms in these studies were categorized as active treatment, placebo treatment, and no treatment. However, the detailed analysis demonstrates that, in some studies, the placebo groups received only placebos, but, in others, they received a combination of active treatment *plus* placebo. A similar problem was realized in the no-treatment groups.

In some studies, patients in the "no treatment" groups were, indeed, not treated (wait-and-see policy), but, in other studies, patients who received standard treatment without placebo are also considered as "no-treatment" patients. These differences, which are important for further discussion, are illustrated in Table I (**p. xx**). Type-1 trials include an active-treatment group, a placebo group, and an observation-only

group. Type-2 trials include an experimental-treatment group, a standard-treatment group plus additional placebo (= placebo group), and a standard-treatment group *without* additional placebo (= standard treatment).

The presence of an observational group in type-1 trials creates a number of risk factors, each of which could distort the study results. One of these risk factors is that patients, once randomised into the non-treatment group, either refuse to participate or seek active treatment outside the study, thereby violating the study conditions. If those patients do not choose either one of these "escape" possibilities, they are fully aware of being left without any treatment, in contrast to their fellow participants in one of the other treatment groups. This awareness can be regarded as a further risk factor.

The type-2 study design used in the meta-analysis is not sufficient to verify the power of placebo. This type of study examines whether the administration of a placebo can enhance the properties of an active treatment or not. If this enhancement does not exist, as described in the present meta-analysis, one cannot conclude that placebo has no effect at all. It is quite possible that the maximal achievable effect has already been induced by the comprehensive features of the active treatment, itself.

Another critical point is the blinding of studies. When the therapist, as well as the patient, is blinded in a study, the double blinding is usually explicitly mentioned in the methods section. Only a few of the studies included in Hróbjartsson's and Goetzsche's meta-analysis mentioned double-blinding. Apart from that, double-blinding could only have been realised in the type-2 studies, as type-1 studies included an untreated group. Consequently, it can be assumed that the majority of the included studies were either single blinded or not blinded at all. There is a tremendous difference in the information provided to a patient after randomisation when the therapist is blinded versus being not blinded. Blinding the therapist principally ensures that each patient in both treatment groups receives the same information. De-blinding the therapist increases the risk that the information given to the patients in the two study arms will be dissimilar, leading to the discussed effects.

Importance of the findings and conclusions

When looking at Hróbjartsson's and Goetzsche's findings, one needs to take into consideration the size and the number of studies evaluated in their meta-analysis, as well as the intensity of the clinical problem. With the exception of the pain studies, the number of studies per indication, as well as the number of patients per study, is rather small. Hróbjartsson and Goetzsche report that essentially no effect can be observed in either of the chosen conditions – neither with the placebo nor the control treatment. This leads them to conclude that there is no placebo effect .

In pain studies, the intensity of the pain was only marginal, since the active treatment showed virtually no effect. In our opinion, valid proof of the absence or presence of an effect seems very questionable due to three problems: the size of the included studies was small, the number of patients per study was small, and the intensity of the investigated problem was marginal. Missing proof of an effect does not inevitably mean that there is none.

Table I: Types of studies and treatments which were included in the meta-analysis. N. B.: "No treatment" includes the possibility that standard treatment was given without additional placebo.

Term used in the meta-analysis	**"Placebo treatment" (p-T)**	**"No treatment" (n-T)**	**"Active treatment" (a-T)**
Type-1 study	Placebo	Observation	Active treatment
Type-2 study	Standard treatment *plus* placebo	Standard treatment *without* placebo	Experimental treatment

Table II: Model of the components of the placebo and other therapies. Proposed model of the components of therapeutic interventions, including the way they are mediated and the lev-els of perception. In day-to-day practice, the doctor is convinced that s/he is aware of administering either active treatment or placebo, while the patient usually believes s/he is getting active treatment. In open (unblinded) studies – not shown here – it is impossible to inform a patient that s/he will be treated with a placebo. Therefore, we assume that both the process and the contents of information in open studies are comparable to the process and content of information in day-to-day practice. An important difference between day-to-day practice and experimental situations, such as clinical studies, is the process of information, i.e., informed consent is mandatory in experimental situations. In these situations, patients will receive two different types of information, one when the informed consent is obtained and another when the patients are treated.

Components of any inter-vention	Mediated mainly by:	Levels of perception	In day-to-day practice∗		In single-blind studies∗		In double-blind studies†	
			Active treatment	Placebo treatment	Active treatment	Placebo treatment	Active treatment	Placebo treatment
Relationship of trust	**non-verbal or verbal signs**	**emotional**	**necessary**	**necessary**	**necessary**	**necessary**	**necessary**	**necessary**
Information	**verbal communi-cation**	**explicit**	**in cognitive agreement with doctor's assumption‡**	**in cognitive dissonance with doctor's assumption**	**in cognitive agreement with doctor's assumption**	**in cognitive consonance or dissonance with doctor's assumption**	**in cognitive uncertainty**	**in cognitive uncertainty**
Vehicle	**physical-chemical interven-ion**	**physical-chemical intervent-ion**	**specific physical-chemical effectiveness assumed**	**no specific physical-chemical effectiveness assumed**	**specific physical-chemical effectiveness assumed**	**no specific physical-chemical effectiveness assumed**	**specific physical-chemical effectiveness assumed**	**no specific physical-chemical effectiveness assumed**

∗ The problem with single-blind studies is that the information is asymmetrically distributed between doctor and patient. As in day-to-day practice, the doctor usually has more information than the patient. Therefore, the information provided to patients in the placebo group is in cognitive dissonance rather than in cognitive consonance with the therapist's assumption, while the information provided to the patient in active therapy is in cognitive agreement because the therapist is tempted to provide positive information. By doing so, he will unblind the type of therapy administered.

† The effect of the information in double-blind studies will be different, depending on whether blinding of the doctor and/or of the patient is maintained or not during treatment (which is usually neither assessed nor described).

‡ We prefer the expression "assumption" to the expression "knowledge" to underline the fact that today's knowledge can be tomorrow's error See the corn-oil example.

Model of the components of the placebo and other therapies

Based on the evidence that induced the hypothesis of "knowledge framing" and on the results of the critical appraisal of the meta-analysis, a model is suggested which describes three components of the placebo effect and assumptions on how these components are mediated and perceived. The three components are: the relationship of trust between doctor and patient, the information provided to the patient, and the physical/chemical vehicle given to the patient.

The first component, the *relationship* of trust between therapist and patient, includes previous experience, personal understanding, recommendations by others, the asymmetric distribution of information, and the surroundings in which the encounter between therapist and patient takes place.

The second component is the *information* itself. It includes expected and not expected, motivating and demotivating information, as well as good and bad news. Identical words can convey different informational content, depending on several variables. Such a variable is the current frame of mind of the person providing and the person receiving the information, or the existing relationship of trust. The multitude of factors involved in this component demonstrate its complexity, making it difficult to find a quantitative description.

The third component is the *vehicle* which is mediated by various types of physical or chemical intervention (e.g., surgery, pharmacological therapy, or speech in psychotherapy). Successful physical or chemical signal transmission (seeing, hearing, feeling, smelling, tasting) is a prerequisite for the perception of the information provided.

According to our model, the component "relationship of trust" is mediated mainly by verbal or non-verbal signs. The "information" is mediated by verbal communication and the "vehicle", by the physical/chemical intervention. The relationship of trust is perceived on an emotional level, the information on an explicit level, and the vehicle on a physical/chemical level. It should be emphasized that the ways these components are mediated by the therapist and perceived by the patient do not explain a causal relationship between one of the components and the observed effect.

The following examples illustrate the progress in medicine (i.e. changing medical assumptions) in relation to the effectiveness of the vehicle used: Thirty years ago, a therapy which coated the intestinal mucosa with a buffered solution was considered the standard therapy for duodenal ulcer. Later on, surgical vagotomy, and, years later, the administration of proton-pump inhibitors became the treatment of choice. Today, antibiotics are considered the state-of-the-art treatment.

In the early seventies, corn oil was used as a placebo medication in studies investigating the effect of cholesterol-lowering agents in heart disease.[15] Twenty years later, it is assumed that corn oil can reduce low-density lipoprotein, a factor known to be associated with coronary heart disease.[16]

In the first interpretation of our systematic review on immunotherapy of renal cell cancer, we assumed that interferon caused the observed prolongation of life. The critical analysis supported the assumption that a psychological effect, "knowledge framing", may have contributed to cause the marginal prolongation of survival. These examples demonstrate the relativity of what is considered "state of the art". The same

vehicle may function as an active treatment or as a placebo, depending on the scientific community's[c] current interpretation.

In Table II (**p. xx**), we summarize the components of placebos, the ways they are mediated by doctors, and the levels at which they are perceived by patients. The complexity of the system is shown by the variable significance of these components, depending on the special setting. In active treatment in day-to-day practice, the doctor assumes a specific physical/chemical effect of the administered vehicle (which is different when a placebo is administered). In this situation, the patient's information is given in cognitive agreement with the doctor's assumption (which is also different in placebo therapy). This table also demonstrates that the conditions are different in single-blind and in double-blind studies. The situation is rather clear in double-blind studies if neither doctor nor patient is unblinded by additional information associated with any of the treatments. The effects of knowledge framing cannot be excluded in single-blind studies in which the information is asymmetrically distributed between doctor and patient.

Discussion

The three examples of the post-randomisation informed consent, the meta-analysis of immunotherapy of advanced renal cell cancer, and the meta-analysis of triple-armed, placebo-controlled trials, demonstrate that the known physical and chemical effects do not completely explain the observed treatment results. Additional effects, which are usually summarized in clinical studies as placebo effects, also have to be considered. The aim of placebo-controlled trials is to differentiate between effects which are mediated by the investigated experimental treatment, like a new drug, and by other, so-called non-specific or "soft effects". The labelling as "soft" effects may be not justified, as these "soft" effects are definitely more difficult to quantify than physical or chemical effects. Therefore, it is quite possible that the lack of quantitative data on "soft effects" is explained by the difficulties encountered in assessing such effects.

According to our understanding, placebo effects are not limited to an imitation intervention, but include three essential components: the relationship of trust between doctor and patient, the information given to the patient, and the vehicle used. These three components seem to apply to any type of treatment. Both settings, active therapy in day-to-day clinical practice and placebo therapy in a clinical trial, require a relationship of confidence, verbal or non-verbal information, and a physical or chemical vehicle which supports the transmission of the information. When active therapy is administered, the doctor assumes a specific physical or chemical effect of the treatment. In double-blind studies, the doctor is left in a state of uncertainty. The patient's information will depend on the doctor's knowledge and, accordingly, will be different in the two above-mentioned settings. A concept which is similar to our model has recently been published by Kaptchuk,[17] who suggested five components of the

c. When the heterogeneity of treatments which produce favourable outcomes in the same disease is critically analysed, one might conclude that the considered physical/chemical treatment may be only one of the factors which influencing the outcome, unless other factors, such as "knowledge framing", can be excluded.

placebo effect: patient, practitioner, patient-practitioner interaction, nature of the illness, and treatment setting.

Our first component, the relationship of trust, refers to Kaptchuk's component of the patient's characteristics. Several experiments confirm that the patient's expectations determine the outcomes of interventions. Depending on the information provided, asthma patients believe that inert substances have a bronchodilator or a bronchoconstrictor effect.[18,19,20] Healthy volunteers observed differing effects on gastric motility according to induced expectations.[21] Adherence to the prescription is another factor which influences the outcome. Adherence to placebo was associated not only with symptom relieve, but also with length of survival.[22,23,24] It is important to note that even the patient's preferences for a special type of intervention – respected in shared decision making in day-to-day practice – influences the treatment outcomes.[25,26,27]

Kaptchuk's component of patient-practitioner interaction can be subsumed in part to our component of trust. There are several studies[28,29,30] which confirm the favourable influence of the agreement between doctor and patient on clinical outcomes. The success of medical treatment, not only of alternative medicine, cannot be strictly limited to "objective" criteria when 50% of patients never receive a firm diagnosis in conventional medicine.[31,32]

The second component of our model, the information, refers to the practitioner's characteristics, as well as to the patient-practitioner interaction of Kaptchuk's concept. Heroic, enthusiastic, or optimistic attitudes of the doctor have been compared with neutral or doubtful behaviour in clinical studies. These studies demonstrated a significant conditioning effect in the treatment of pain, psychiatric illness, hypertension, obesity, and perimenopausal symptoms (referenced in 17). Two reviews on the role of information provide some support for the mentioned placebo effect, but also identified the need for more research in this area.[33,34] The lack of solid data on the influence of information is not surprising, as it is rather difficult – according to ethical rules – to test the influence of information in a clinical trial. Such experiments require providing different information to otherwise identically-treated patients. Such studies are difficult to design and conduct. The component of patient information is also influenced by the doctor's expectations. Only few references[35,36,37] exist on the influence of physician expectations on treatment results. Systematic investigation of the topic is still lacking.

The third component of our model, the vehicle, corresponds to Kaptchuk's component of treatment and setting. It is known that the intensity of the treatment (needle or tablet)[38,39] and the frequency of placebo treatments[40] influence the effectiveness of the therapy. Patients usually expect to get a "vehicle", and the existing data suggest that active interventions produce better outcomes than no treatment at all.[2,41] Two randomised trials indicate that more intensive treatments – regardless of their specificity – produce better results than less intensive treatments.[42,43] These data suggest that the function of the "vehicle" seems to be an important component of any treatment intervention.

There is sufficient evidence supporting the assumption that the effects of active treatment can be augmented by several components of a placebo effect. We mentioned that the aim of a well-designed clinical trial is the identification of the "true" physical or chemical effect. Additional effects, like placebo effects, would disturb the goal of the test and have to be controlled or eliminated. This concept explains the negative connotation of the terms "placebo" and "placebo effect".

In day-to-day practice, additional effects which amplify the "true" physical or chemical effect are welcomed. We try to avoid the term "placebo" in day-to-day treatment. In this situation, we prefer the term "knowledge framing" and consider the concepts, but not the effects, of "knowledge framing" and of "placebo" to be different. This may be expressed in four assumptions. First, a placebo effect is considered to be an "as-if-therapy" effect, while the effect of knowledge framing is accepted as one of several components in the overall effect of a health-care intervention. Second, placebo is not thought of as a specific physical effect; knowledge framing is considered a specific effect of the information provided. There are, indeed, data supporting the view that placebo effects – not the placebo itself – are organ-specific,[44] which agrees with our concept of knowledge framing. Third, the placebo effect is thought to lie below the threshold of standard therapy, while the effect of knowledge framing is assumed to lie above that threshold.

Fourth, the use of placebos is limited to clinical trials, whereas knowledge framing is not; knowledge framing is part of any doctor-patient encounter.

The information derived from the careful analysis of several clinical trials may be used for recommendations on the design of clinical trials. If the patient's information and the vehicle are really such powerful components as proposed here, future clinical trials should not include a study arm in which one group of patients is left untreated. In addition to the differences in the potentially-effective components (no physical/chemical agent, no vehicle, different information for patients in the active treatment arm?), these patients are more likely to seek treatment outside of the clinical trial because they know that they are not getting an available active treatment.

For similar reasons, we recommend avoiding semi-blind clinical trials. If patients are properly informed in a semi-blind clinical trial, they will know that the doctor (but not the patient) is aware of the patient's allocation to the active treatment or the placebo group, but will not pass his/her knowledge on to the patient. This asymmetric distribution of information is likely to influence the relationship of trust between doctor and patient. Alternatively, it has to be discussed that some doctors may not provide complete information to patients in a semi-blind trial to avoid such a conflict. As a research tool, such semi-blind trials carry risks which can be avoided by using either double-blind or open (not-blinded) study designs.

These examples again confirm the potential power of information in clinical trials. As the provided information is not confined to the "informed consent", but includes all types of patient information, it will be difficult to control for this powerful component. Nevertheless, attempts have to be made to standardise the essential component of information in clinical trials. A first step in this direction may be the support of scientific projects to generate the scientific data which are needed for standardisation of informed consent.

The essential message we wish to convey here is related to the change in our attitude towards so-called placebo effects. Placebo effects have to be discussed as important effects in clinical research. The conceptually different, but otherwise identical, effects of knowledge framing are part of any doctor-patient encounter. A more comprehensive understanding of the placebo effect will help install knowledge framing as an integrative part of effective medicinal practice, rather than viewing it as an illegitimate trick to please difficult patients.[45,46,47] There is an important difference between research and standard medical care concerning non-physical/non-chemical treatment effects. In research, it is necessary to reduce the observed overall effect by the placebo effect. In standard medical care, we may accept the overall effect, knowing from research that only part of it will be caused by physical/chemical effects.

This changed understanding of placebo and knowledge framing effects will have some impact on the evaluation of medical services from an ethical, medical, economical and legal point of view.

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